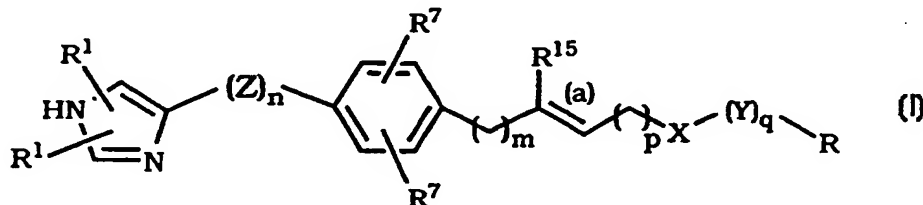




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(21) International Application Number: PCT/US98/23225 (22) International Filing Date: 5 November 1998 (05.11.98) (30) Priority Data: 08/966,264 7 November 1997 (07.11.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/966,264 (CIP) Filed on 7 November 1997 (07.11.97) (71) Applicant (for all designated States except US): SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ASLANIAN, Robert, G. [US/US]; 144 Philip Drive, Rockaway, NJ 07866 (US). McCORMICK, Kevin, D. [US/US]; 5 Pace Drive, Edison, NJ 08820 (US). PIWINSKI, John, J. [US/US]; 6 Saddle Ridge Drive, Lebanon, NJ 08833 (US).		(74) Agents: JEANETTE, Henry, C. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: PHENYL-ALKYL-IMIDAZOLES AS H3 RECEPTOR ANTAGONISTS



(57) Abstract

Disclosed are novel phenyl-alkyl-imidazoles of formula (I) wherein R¹, R⁷, m, n, p, q, X, Y, Z, R and R¹⁵ are as defined in the specification. Also disclosed are pharmaceutical compositions comprising the compounds of formula (I). Further disclosed are methods of treating allergy, inflammation, hypotension, glaucoma, sleeping disorders, states of hyper and hypo motility of the gastrointestinal tract, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines by administering compounds of formula (I). Also disclosed are methods for treatment of upper airway allergic responses comprising administering a compound, or salt or solvate thereof, of formula (I) in combination or admixture with a histamine H₁ receptor antagonist.

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PHENYL-ALKYL-IMIDAZOLES AS H₃ RECEPTOR ANTAGONISTS10 FIELD OF THE INVENTION

The present invention relates to novel phenyl-alkyl-imidazoles having valuable pharmacological properties, especially CNS activities and activity against inflammatory disease. Compounds of this invention are antagonists of the H₃ receptor.

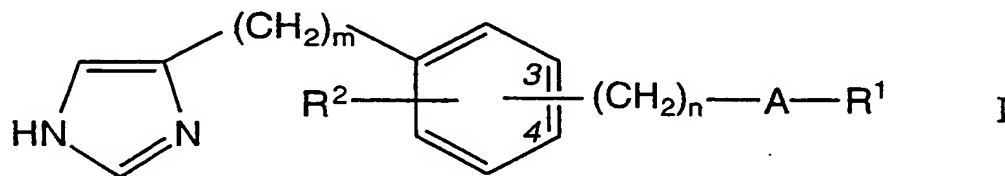
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BACKGROUND OF THE INVENTION

European Patent Application No. 0 420 396 A2 (Smith Kline & French Laboratories Limited) and Howson et al., *Bioorg. & Med. Chem. Letters*, Vol. 2 No. 1 (1992), pp. 77-78 describe imidazole derivatives
20 having an amidine group as H₃ agonists. Van der Groot et al. (*Eur. J. Med. Chem.* (1992) Vol. 27, pp. 511-517) describe isothioureia analogs of histamine as potent agonists or antagonists of the histamine H₃ receptor, and these isothioureia analogs of histamine overlap in part with those of the two references cited above. Clapham et al. ["Ability of Histamine H₃
25 Receptor Antagonists to improve Cognition and to increase Acetylcholine Release *in vivo* in the Rat", British Assn. for Psychopharmacology, July 25-28 1993, reported in *J. Psychopharmacol.* (Abstr. Book), A17] describe the ability of histamine H₃ receptor antagonists to improve cognition and to increase release of acetylcholine *in vivo* in the rat. Clapham et al.
30 ["Ability of the selective Histamine H₃ Receptor Antagonist Thioperamide to improve Short-term Memory and Reversal Learning in the Rat", *Brit. J. Pharm. Suppl.*, 1993, 110, Abstract 65P] present results showing that thioperamide can improve short-term memory and reversal learning in the rat and implicate the involvement of H₃ receptors in the modulation of

cognitive function. Yokoyama et al. ["Effect of thioperamide, a histamine H₃ receptor antagonist, on electrically induced convulsions in mice", *Eur. J. Pharmacol.*, vol. 234 (1993), pp. 129-133] report how thioperamide decreased the duration of each phase of convulsion and raised the electroconvulsive threshold, and go on to suggest that these and other findings support the hypothesis that the central histaminergic system is involved in the inhibition of seizures. International Patent Publication No. WO9301812-A1 (SmithKline Beecham PLC) describes the use of S-[3-(4(5)-imidazolyl)propyl]isothiourea as a histamine H₃ antagonist, especially for treating cognitive disorders, *e.g.* Alzheimer's disease and age-related memory impairment. Schlicker et al. ["Novel histamine H₃ receptor antagonists: affinities in an H₃ receptor binding assay and potencies in two functional H₃ receptor models"] describe a number of imidazolylalkyl compounds wherein the imidazolylalkyl group is bonded to a guanidine group, an ester group or an amide group (including thioamide and urea), and compare these to thioperamide. Leurs et al. ["The histamine H₃-receptor: A target for developing new drugs", *Progr. Drug Res.* (1992) vol. 39, pp. 127-165] and Lipp et al. ["Pharmacochemistry of H₃-receptors" in *The Histamine Receptor*, eds.: Schwartz and Haas, Wiley-Liss, New York (1992), pp. 57-72] review a variety of synthetic H₃ receptor antagonists, and Lipp et al. (*ibid.*) have defined the necessary structural requirements for an H₃ receptor antagonist.

WO 95/14007 claims H₃ receptor antagonists of the formula



wherein

A is selected from $-\text{O}-\text{CO}-\text{NR}^1-$, $-\text{O}-\text{CO}-$, $-\text{NR}^1-\text{CO}-\text{NR}^1-$, $-\text{NR}^1-\text{CO}-$, $-\text{NR}^1-$, $-\text{O}-$, $-\text{CO}-\text{NR}^1-$, $-\text{CO}-\text{O}-$, and $-\text{C}(:\text{NR}^1)-\text{NR}^1-$;

the groups R¹, which may be the same or different when there are two or three such groups in the molecule of formula I, are selected from

hydrogen, and lower alkyl, aryl, cycloalkyl, heterocyclic and heterocycl-

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alkyl groups, and groups of the formula $-(CH_2)_y-G$, where G is selected from CO_2R^3 , COR^3 , $CONR^3R^4$, OR^3 , SR^3 , NR^3R^4 , heteroaryl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y is an integer from 1 to 3;

5 R^2 is selected from hydrogen and halogen atoms, and alkyl, alkenyl, alkynyl and trifluoromethyl groups, and groups of the formula OR^3 , SR^3 and NR^3R^4 ;

R^3 and R^4 are independently selected from hydrogen, and lower alkyl and cycloalkyl groups, or R^3 and R^4 together with the intervening
10 nitrogen atom can form a saturated ring containing 4 to 6 carbon atoms that can be substituted with one or two lower alkyl groups;

with the proviso that, when y is 1 and G is OR^3 , SR^3 or NR^3R^4 , then neither R^3 nor R^4 is hydrogen;

the group $-(CH_2)_n-A-R^1$ is at the 3- or 4-position, and the group R^2
15 is at any free position;

m is an integer from 1 to 3;

and n is 0 or an integer from 1 to 3;

or a pharmaceutically acceptable acid addition salt thereof;

or a pharmaceutically acceptable salt thereof with a base when G is

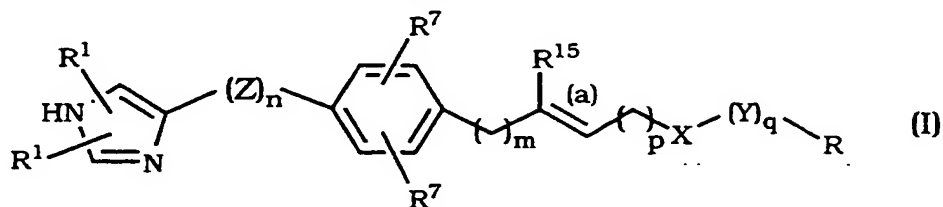
20 CO_2H ; including a tautomeric form thereof.

US Application Serial. No. 08/689951 filed August 16, 1996 and U.S. Application Serial No. 08/909319 filed August 14, 1997 disclose compositions for the treatment of the symptoms of allergic rhinitis using a combination of at least one histamine H_1 receptor antagonist and at least
25 one histamine H_3 receptor antagonist.

In view of the art's interest in compounds which affect the H_3 receptors, novel compounds having antagonist activity on H_3 receptors would be a welcome contribution to the art. This invention provides just such a contribution by providing novel compounds having H_3 antagonist
30 activity.

SUMMARY OF THE INVENTION

The present invention provides a compound of the formula I



or a pharmaceutically acceptable salt or solvate thereof, wherein:

- 5 the double bond (a) is E or Z (that is the double bond to the carbon atom having the R¹⁵ substituent is of the E or Z configuration);

 each R¹ is independently selected from the group consisting of hydrogen, lower alkyl, trihalomethyl, phenyl and benzyl;

- each R⁷ is independently selected from the group consisting of
10 hydrogen, lower alkyl, halogen, trihalomethyl, NR¹⁰R¹¹, or a group OR¹⁰, whereby R¹⁰ and R¹¹ are independently selected from hydrogen, lower alkyl or trihalomethyl;

- X is -CONR⁵-, -SO₂-, -S-, -CO-, -COO-, -CN(OR⁵)NR⁵-,
-C(NR⁵)NR⁵-, -SONR⁵-, -SO₂NR⁵- and, provided p is not zero, X may also
15 be -O-, -NR⁵-, -NR⁵CONR⁵-, -OCONR⁵-, -O-CO- or -NR⁵CO-;

 Y is C₁-C₃-alkyl, optionally substituted at any carbon atom of the group by one substituent R⁵;

 Z is C(R¹)₂; wherein no more than two R¹ groups are other than hydrogen;

- 20 n is 1 or 2;
 m is 0 or 1;
 p is 0 or 1;
 q is 0 or 1;

- R is selected from C₃ to C₇ cycloalkyl, heterocyclic groups, aryl or
25 heteroaryl, wherein said R groups are optionally substituted with 1-3 substituents as defined below;

 each R⁵ independently represents hydrogen, lower alkyl or polyhaloloweralkyl; and

 R¹⁵ represents H or lower alkyl (e.g., methyl).

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A further feature of the invention is pharmaceutical compositions containing as active ingredient a compound of the formula I defined above (or a salt, or a solvate or tautomer) together with a pharmaceutical carrier or excipient.

- 5 Further features of the invention are methods for treating inflammation, allergy, diseases of the GI-tract, cardiovascular disease, or disturbances of the central nervous system, which comprise administering to a patient suffering from the corresponding disease (i.e., a patient in need of such treatment) an effective amount of a compound of the formula
- 10 I defined above (or a salt, solvate or tautomer thereof). For example, a feature of this invention is a method of treating allergy, inflammation, hypotension, glaucoma, sleeping disorders, states of hyper and hypo motility of the gastrointestinal tract, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines,
- 15 comprising administering an effective amount of a compound of formula I (or a salt, solvate or tautomer thereof) to a patient in need of such treatment.

- Another feature of this invention is a method for treating inflammation, which comprises administering to a patient suffering from
- 20 inflammation an effective amount of a compound of formula I (or a salt, solvate or tautomer thereof) to a patient in need of such treatment.

- Another feature of this invention is a method for treating allergy, which comprises administering to a patient suffering from allergy an effective amount of a compound of formula I (or a salt, solvate or tautomer
- 25 thereof) to a patient in need of such treatment.

- Another feature of this invention is a method for treating diseases of the GI-tract, which comprises administering to a patient suffering from a disease of the GI-tract an effective amount of a compound of formula I (or a salt, solvate or tautomer thereof) to a patient in need of such treatment.

- 30 Another feature of this invention is a method for treating cardiovascular disease, which comprises administering to a patient suffering from cardiovascular disease an effective amount of a compound

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of formula I (or a salt, solvate or tautomer thereof) to a patient in need of such treatment.

Another feature of this invention is a method for treating disturbances of the central nervous system, which comprises
5 administering to a patient suffering from disturbances of the central nervous system an effective amount of a compound of formula I (or a salt, solvate or tautomer thereof) to a patient in need of such treatment.

The invention also includes the aspect of using the compounds of formula I in combination with a histamine H₁ receptor antagonist for
10 treatment of allergy-induced airway (e.g., upper airway) responses.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the formula I can exist in tautomeric forms by virtue of the imidazole ring: the N-hydrogen atom can tautomerize from one
15 nitrogen atom to the other of that ring. When q is 1 and Y is a substituted alkyl group, or when one R¹ substituent of each (Z)_n group is other than H, the compounds of formula I will have asymmetric carbon atoms and will exist in different forms due to such chiral center. All such isomers including diastereomers and enantiomers are covered by the invention.

20 The compounds of the invention are basic and form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and
25 carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide,
30 potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their corresponding salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are

otherwise equivalent to their corresponding free base forms for purposes of this invention.

The compounds of Formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

Numerous chemical substances are known to have histamine H₁ receptor antagonist activity. Many useful compounds can be classified as ethanolamines, ethylenediamines, alkylamines, phenothiazines or piperidines. Representative H₁ receptor antagonists include, without limitation: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine (also known as SCH-34117), diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine. Other compounds can readily be evaluated to determine activity at H₁ receptors by known methods, including specific blockade of the contractile response to histamine of isolated guinea pig ileum. See for example, WO98/06394 published February 19, 1998.

For example, the H₃ antagonists of this invention can be combined with an H₁ antagonist selected from astemizole, azatadine, azelastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, carebastine, descarboethoxyloratadine (also known as SCH-34117), diphenhydramine, doxylamine, ebastine, fexofenadine, loratadine, levocabastine, mizolastine, norastemizole, or terfenadine.

Also, for example, the H₃ antagonists of this invention can be combined with an H₁ antagonist selected from, azatadine, brompheniramine, cetirizine, chlorpheniramine, carebastine, descarboethoxy-

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loratadine (also known as SCH-34117), diphenhydramine, ebastine, fexofenadine, loratadine, or norastemizole.

Representative combinations include: the H₃ antagonists of this invention with loratadine, H₃ antagonists of this invention with
5 descarboethoxyloratadine, H₃ antagonists of this invention with fexofenadine, and H₃ antagonists of this invention with cetirizine.

Those skilled in the art will know that the term "upper airway" means the upper respiratory system--i.e., the nose, throat, and associated structures.

10 When used herein, unless indicated otherwise, the following terms have the given meanings:

lower alkyl (including the alkyl portions of lower alkoxy) -- represents a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms, preferably from 1 to 4;

15 aryl -- represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with 1 to 3 groups, each optional substituent being
20 independently selected from the group consisting of lower alkyl, halogen, trihalomethyl, CN, NO₂, OR¹⁰ or NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are independently selected from hydrogen, lower alkyl or trihalomethyl; preferred aryl groups include 1-naphthyl, 2-naphthyl and indanyl, and especially phenyl and substituted phenyl;

25 cycloalkyl -- represents a saturated carbocyclic ring having from 3 to 8 carbon atoms, preferably 5 or 6, optionally substituted by 1 to 3 groups independently selected from the group consisting of lower alkyl trihalomethyl and NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are independently selected from hydrogen, lower alkyl or trihalomethyl; said cycloalkyl group
30 optionally being fused to an aryl ring (e.g., phenyl), e.g., cyclohexyl fused to phenyl;

heterocyclic -- represents saturated and unsaturated non-aromatic cyclic organic groups having at least one O, S and/or N atom

interrupting a carbocyclic ring structure that consists of one ring or two fused rings, wherein each ring is 5-, 6- or 7-membered, which ring structure has from 2 to 8, preferably from 3 to 6 carbon atoms; e.g., 2- or 3-pyrrolidinyl, 2-, 3- or 4-piperidinyl, 2- or 3-piperazinyl, 2- or 3-morpholinyl, or 2- or 3-thiomorpholinyl; said heterocyclic group being optionally substituted by 1 to 3 groups independently selected from the group consisting of lower alkyl, trihalomethyl, and $\text{NR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are independently selected from hydrogen, lower alkyl or trihalomethyl, said substituents being bound to carbon atoms (substitutable carbon atoms) in the ring such that the total number of substituents in the ring is 1 to 3; and wherein said heterocyclic ring contains nitrogen atoms, said nitrogen atoms (i.e., the substitutable nitrogen atoms) being optionally substituted with lower alkyl (e.g., alkyl), e.g., 1-N-methylpyrrolidinyl;

halogen – represents fluorine, chlorine, bromine and iodine; and

heteroaryl – represents a cyclic organic group having at least one O, S and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., indolyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or 4-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, and the like; preferred heteroaryl groups are 2-, 3- and 4-pyridyl; said heteroaryl groups being optionally substituted with 1 to 3 groups, each optional substituent being independently selected from the group consisting of lower alkyl, halogen, trihalomethyl, CN, NO_2 , OR^{10} or $\text{NR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are independently selected from hydrogen, lower alkyl or trihalomethyl, said substituents being bound to carbon atoms (substitutable carbon atoms) in the ring such that the total number of substituents in the ring is 1 to 3.

Compounds of this invention are antagonists of the H_3 receptor. As such, they may be useful for the treatment of various allergic, inflammatory, GI-tract, or cardiovascular diseases. In addition, they possess CNS activity; they may be useful as sleep regulators,

anticonvulsants, cognition enhancers, antidepressants, regulators of hypothalamo-hypophyseal secretions, and the like.

Compounds of formula I include those compounds wherein R^1 is H.

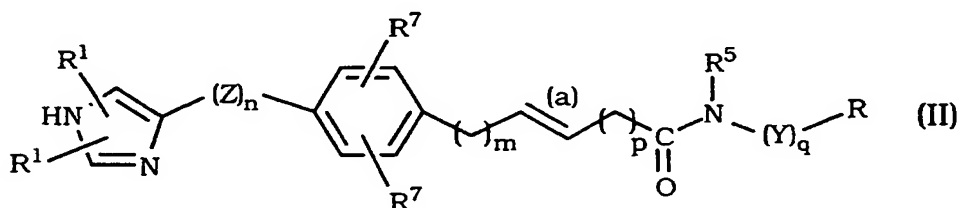
Compounds of formula I also include compounds wherein n is 1.

- 5 Compounds of formula I further include compounds wherein R^1 is H and n is 1.

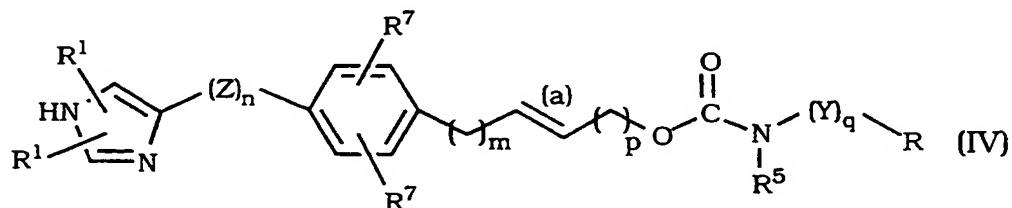
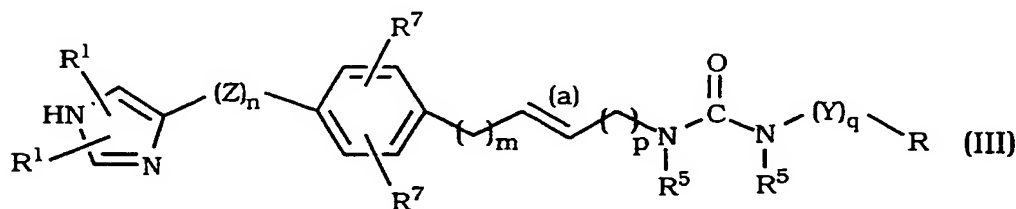
Compounds of formula I additionally include compounds wherein wherein R^1 is H, R^7 is H, and n is 1.

- 10 In addition, compounds of formula I include compounds wherein R^{15} is hydrogen.

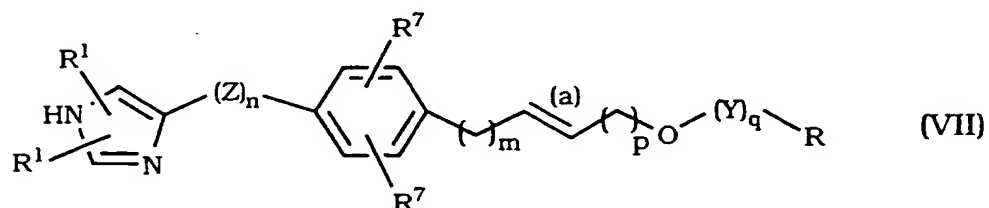
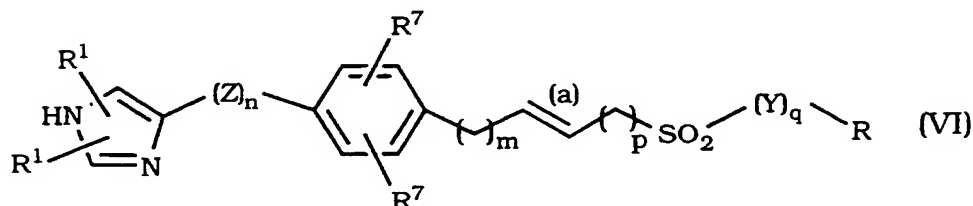
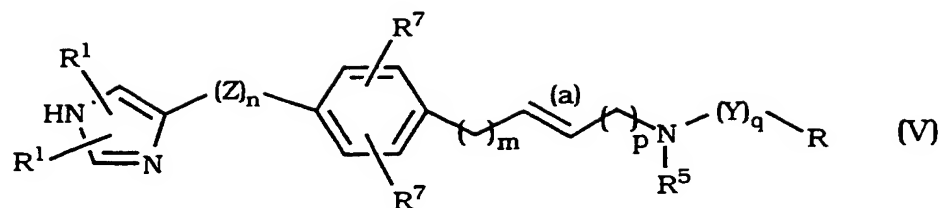
Preferred compounds of formula I are compounds of the formulae II, III, IV, V, VI, and VII described below.



15



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5

wherein R^1 , R^7 , R , Y , Z , (a) , m , n , p and q are as defined for formula I.

R^1 , R^7 and R^{15} are hydrogen. More preferably, n is 1, and R^1 , R^7 and R^{15} are hydrogen. Particularly preferred are those compounds
 10 wherein n is 1, and R^1 , R^7 and R^{15} are hydrogen, and R is phenyl, pyridyl, substituted phenyl or substituted pyridyl. The preferred substituents in said phenyl or pyridyl groups are halogen, preferably chlorine or fluorine, methoxy, trifluoromethyl, CN or trifluoromethoxy. Preferably there are one or two of said substituents, and each substituent is independently
 15 selected.

For compounds of formula II, m is preferably 0. Most preferred are those compounds of formula II wherein m and p are both 0; q is 0 or 1, and, when $q = 1$, Y is $-\text{CHR}^5\text{CHR}^5-$ with one R^5 being hydrogen and the other as defined for R^5 above. For formulae III and IV m is preferably 0 or
 20 1, p is 1 or 2 and q is 0. For all the above groups of compounds the preferred meaning of R is phenyl or phenyl substituted by one or two of the substituents described above in the definition of aryl. The most preferred substituents are CN, chlorine and fluorine, with chlorine and fluorine being

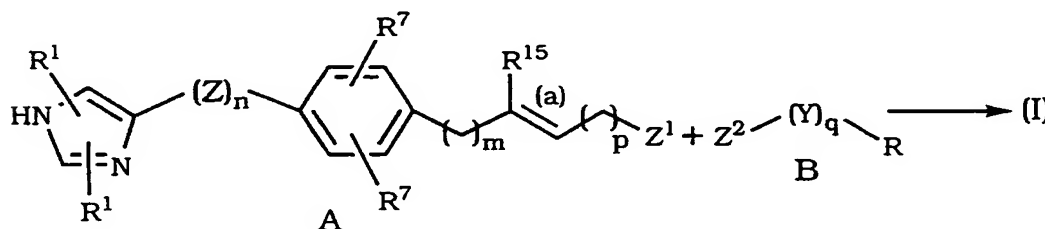
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more preferred. Preferred R-groups are those wherein there is one substituent in the 3-or 4-position, e.g., 4-Cl-phenyl or 3-F-phenyl. If there are two substituents, then the 3,5-substituted compounds are preferred. The preferred meaning of R⁵ is hydrogen. Most preferred are compounds
 5 of formula II.

PREPARATION OF FINAL PRODUCTS

Compounds of the formula I can be prepared by standard methods known in the art. Typical methods appropriate for the preparation of the
 10 compounds of the formula I are illustrated below. In the reaction schemes below only one R¹ or one R⁷ group is shown; however, compounds having the other two groups (i.e., the other R¹ and R⁷) can also be made by the reactions described below. The particular process chosen should not cause significant decomposition elsewhere in the molecule; for
 15 example, removal of a protecting group by hydrogenolysis should not cause the loss of an essential phenylmethyl group.

Basically well known processes such as those described in WO 95/14007 referred to above can, with some modifications, depending on the nature of the group X, be used. The general aspect of the processes
 20 for making the final compounds can be illustrated by the following reaction scheme:

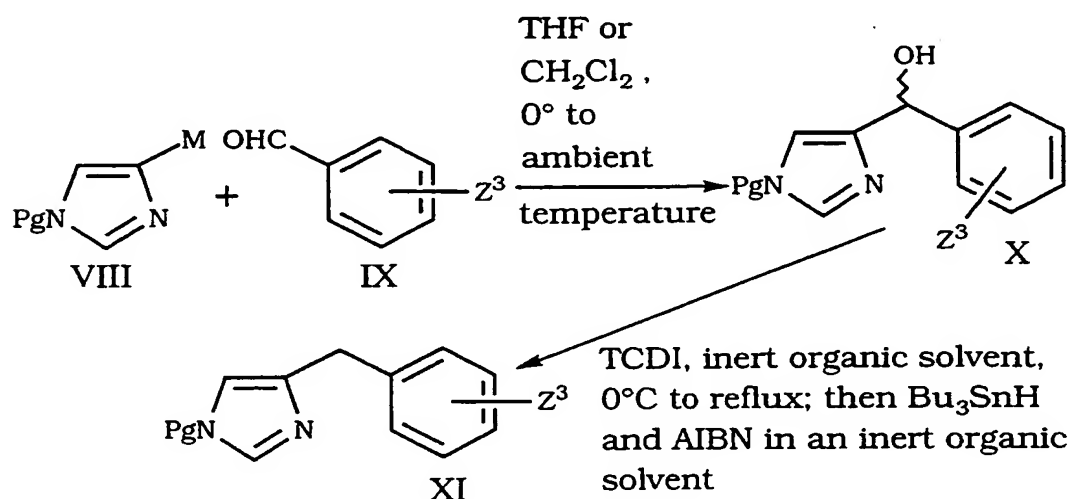


R¹, R⁷, R¹⁵, R, Y, Z, (a), n, m, p and q are as defined for formula I, and Z¹ and Z² are reactive groups selected in such a manner that they
 25 provide the group X in the final compound. Obviously certain groups may have to be protected during the reaction(s). This applies in particular to the NH-group in the imidazole ring. Standard procedures for protection and de-protection may be used.

Starting compounds of formulas A and B are either known or may be prepared according to well known procedures. Reactions 1, 2 and 3 below illustrate the preparation of such compounds.

Reaction 1 (n = 1)

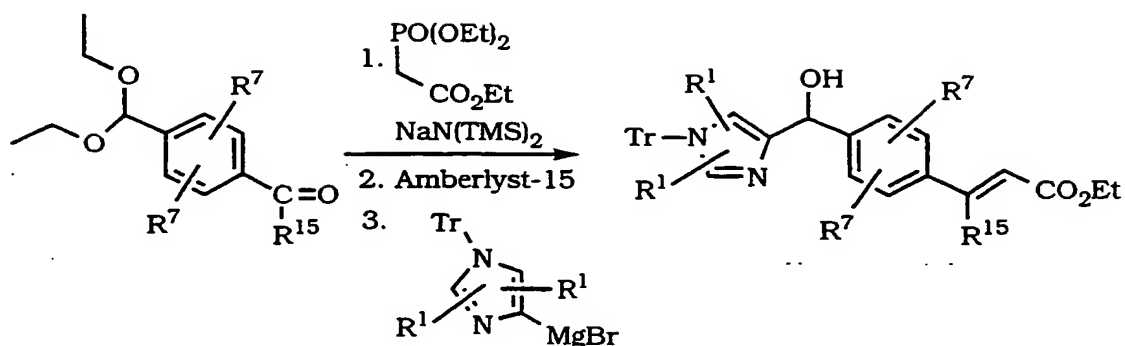
- 5 For n = 1, a metal derivative of an N-protected imidazole (wherein M is e.g., MgBr or MgI, and Pg represents a suitable protecting group, such as, triphenylmethyl) can be reacted with a Z³-substituted-benzaldehyde of the formula IX, and the resulting substituted benzyl alcohol can be reduced, for example, as indicated in the following
- 10 scheme:



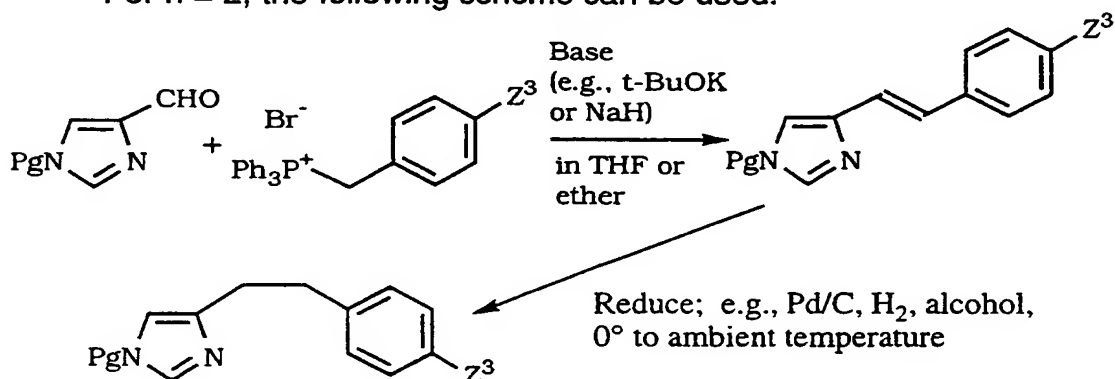
Reaction 2 (n = 1)

- A further method is illustrated in the reaction scheme below. A solution of sodium bis(trimethylsilyl)amide in THF cooled to 0°C is treated with triethylphosphonoacetate. Terephthalaldehyde mono-(diethyl acetal) dissolved in THF is added. The reaction mixture is stirred at 30-40°C for 3-4 h and concentrated. The residue is washed with H₂O and brine, dried and concentrated to give the crude desired compound which is then purified. Tr represents trityl.
- 15

- 14 -

**Reaction 3 (n = 2)**

For n = 2, the following scheme can be used:

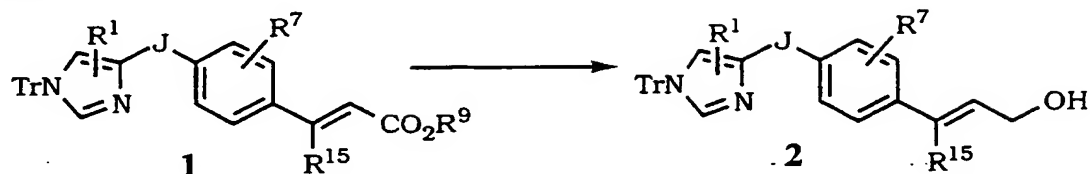


- 5 In the above reaction schemes, wherein the substituents R^1 and R^7 were not included in the formulas, it will be apparent to those skilled in the art that starting compounds wherein such substituents are present could also be used in the reactions described.

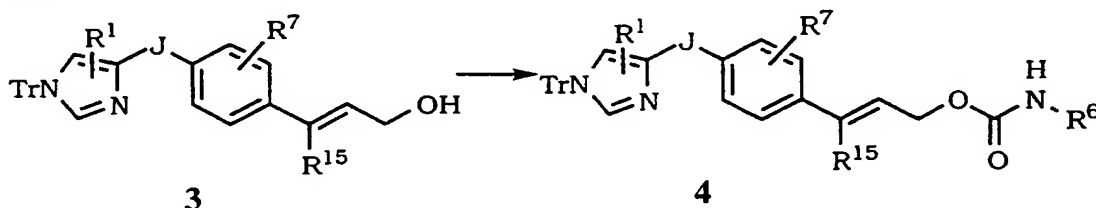
- 10 Z^3 represents a group $-(\text{CH}_2)_m-\text{CR}^{15}=\text{CH}-(\text{CH}_2)_p-\text{Z}^1$ or a group which may be converted into such a group. Ph represents a phenyl group. Other procedures for making compounds of formula A may be found in WO 95/14007. In the following reaction schemes some procedures for preparing the appropriate Z^3 group are shown. Additional examples are found in WO 95/14007.

- 15 The final compounds of this invention are then prepared by reacting a compound A with a compound B followed by the removal of any protecting groups. Such reactions are illustrated in the reaction schemes below. (R^6 represents the group $-(\text{Y})_q-\text{R}$).

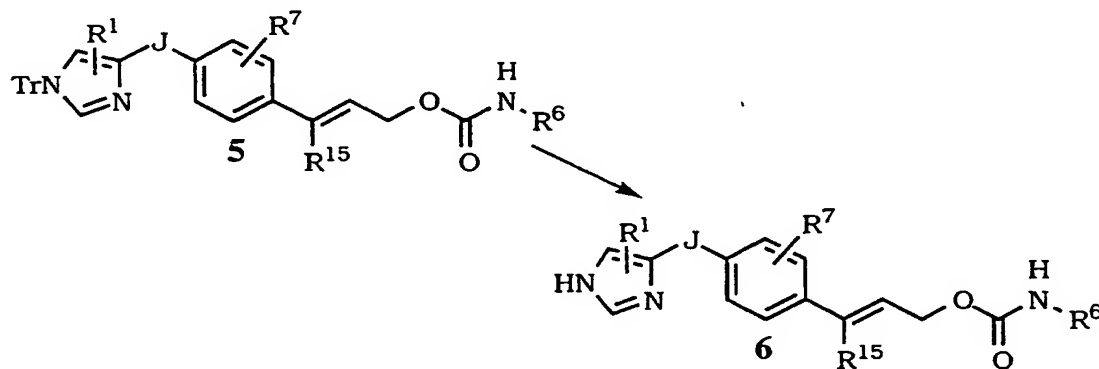
In the reaction schemes below, J represents $(\text{Z})_n$.

Reaction 4 - CarbamatesStep 1

- 5 In Step 1, the ester 1 is dissolved in a suitable solvent such as THF, ether, dioxane, toluene or methylene chloride, preferably THF, and is treated with a reducing agent such as lithium aluminum hydride or diisobutylaluminum hydride, preferably diisobutylaluminum hydride, at a temperature of from -20° C to about 50° C, preferably 0° C, to give the
- 10 alcohol 2. R⁹ is lower alkyl

Step 2

- In Step 2, the alcohol 2 is dissolved in a suitable solvent such as THF, ether, dioxane, toluene or methylene chloride, preferably THF, and is
- 15 treated with an isocyanate R⁶NCO in the presence of a base such as triethylamine or the like at a temperature of from -20° C to 50° C to yield the carbamate 4.

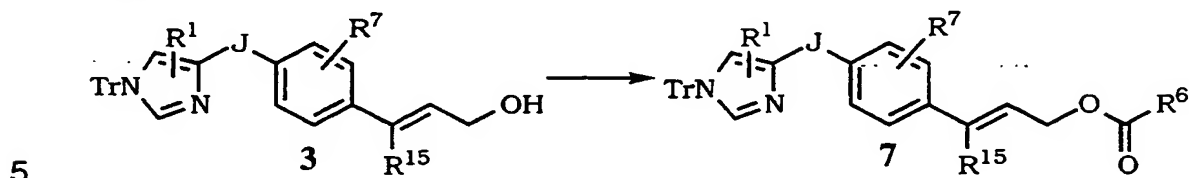
Step 3

- 20 In Step 3, a solution of the carbamate 5 in a suitable alcoholic solvent such as methanol or ethanol, preferably methanol, is treated with a

dilute solution of a mineral acid such as HCl in methanol at a temperature of from 20° C to 100° C, preferably 60° C, to give the product 6 .

Reaction 5 - Esters

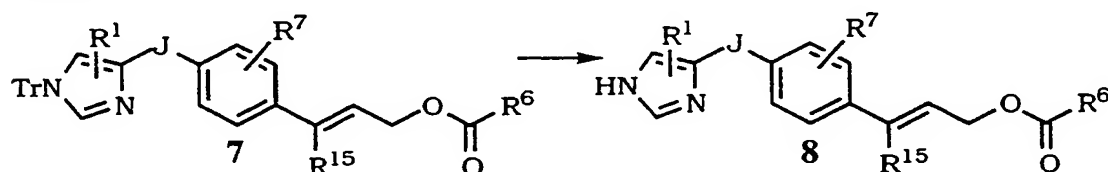
Step 1



In Step 1 the alcohol 3 is reacted with an acid chloride, $\text{R}^6\text{C}(\text{O})\text{Cl}$ in an inert solvent such as ether, THF, dioxane, or methylene chloride, preferably methylene chloride, in the presence of a tertiary amine base such as triethylamine at a temperature of from 0°C to 50°C, preferably 0°C, to give the product 7.

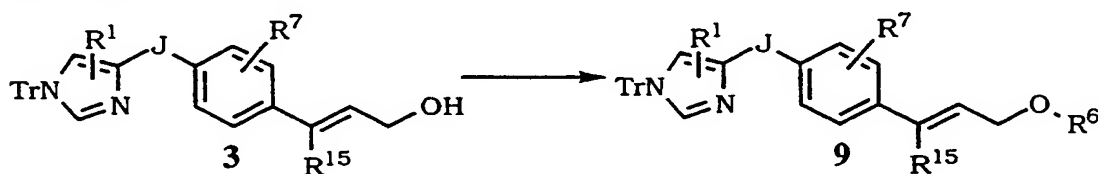
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Step 2



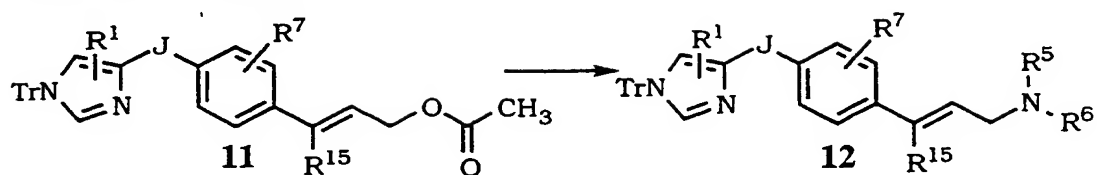
In an analogous manner to that described above, compound 7 is transformed to compound 8.

15 Reaction 6 - Ethers

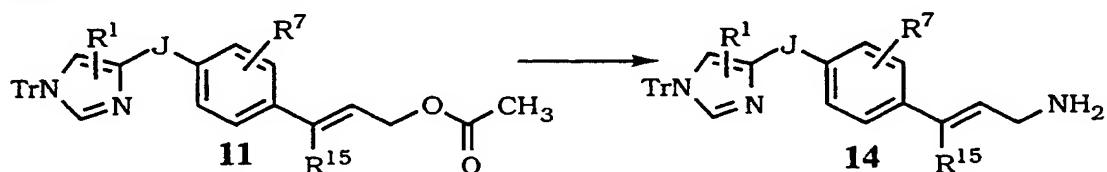


A solution of alcohol 3 in a suitable solvent such as THF or dioxane, preferably THF is added to a suspension of a hydride base such as NaH or KH, preferably NaH, in THF at a temperature of from 0°C to 50°C, preferably 0°C. The reaction is allowed to warm to room temperature for a suitable time to complete alkoxide formation. A suitable alkylating agent, R^6L is added and the reaction stirred for a suitable period of time to complete the reaction. Suitable leaving groups L include Cl, Br, I, and activated forms of OH such as OSO_2CF_3 . Other strong bases can include lithium diisopropylamide and lithium or sodium bistrimethylsilyl-
 20 amide. Deprotection as described above provides the desired compound.

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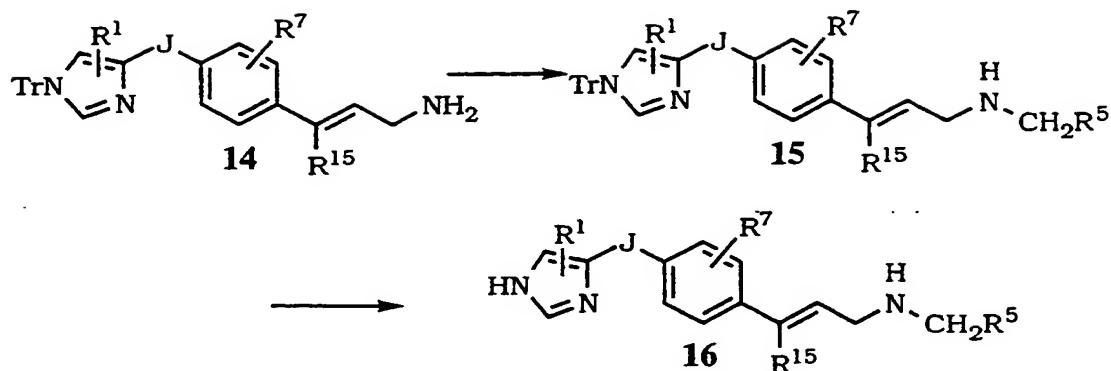
Reaction 7 - Amines

A solution of the acetate **11** and an amine R^5R^6NH in a suitable solvent such as THF, dioxane, toluene, DMF or the like, preferably THF, is treated with a suitable palladium catalyst such as tetrakis(triphenylphosphine)-palladium at a temperature of from $0^\circ C$ to about $100^\circ C$, preferably $65^\circ C$ to give the amine **12**. Deprotection as above gives the amine.

Reaction 8 - Amines10 Step 1

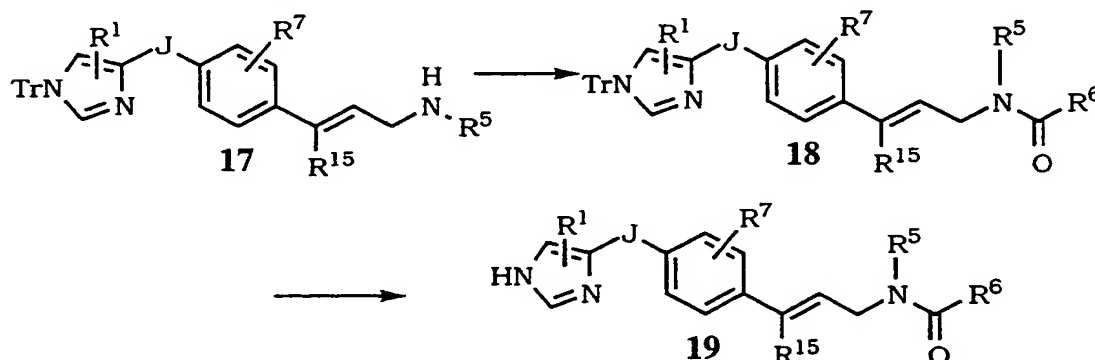
The acetate **11** is treated in an analogous manner to that above substituting trimethylsilylazide for the amine R^5R^6NH to give an allylic azide. Alternatively, instead of trimethylsilylazide, **11** can be treated with NaN_3 in a THF/water mixture in the presence of a palladium catalyst to give the azide. In part 2, the azide is reduced to the amine **14** by dissolution in a suitable organic solvent such as methanol or ethanol, preferably ethanol, adding a hydrogenation catalyst such as Pd/C, PtO_2 , or Raney Ni, preferably Pd/C, and hydrogenating under an atmosphere of hydrogen (16-60 psi, preferably 60 psi) to give **14**. Other reduction methods that can serve equally well include treatment of the azide with $NaBH_4$, $LiBH_4$, $LiAlH_4$, or the like, or with a tertiary phosphine in a water/THF mixed solvent system.

- 18 -

Step 2

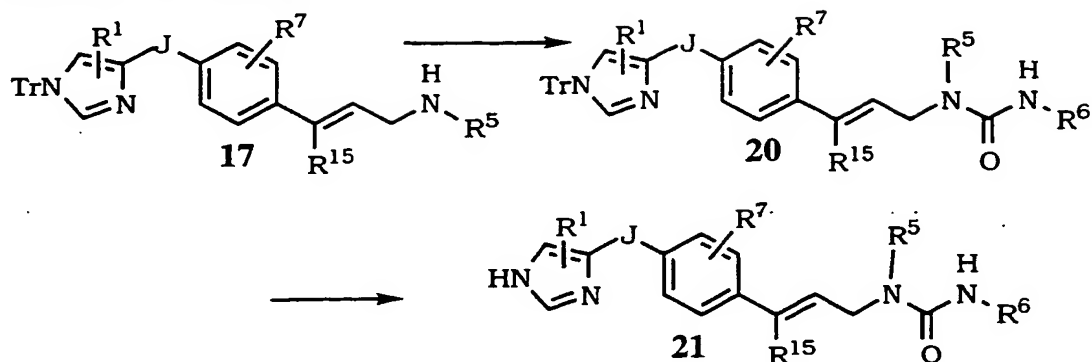
In Step 2, the amine **14** is dissolved in a polar solvent such as methanol, ethanol, or trifluoroethanol and treated with an aldehyde

- 5 R^5CHO or ketone $(R^5)_2CO$ in the presence of powdered molecular sieves at a temperature of from $0^\circ C$ to $80^\circ C$, preferably $22^\circ C$ for a time sufficient to ensure imine formation. A reducing agent such as $NaBH_3CN$ or $Na(AcO)_3BH$, preferably $Na(AcO)_3BH$, is added and the reaction stirred until complete. Deprotection of the amine **15** gives the product **16**.

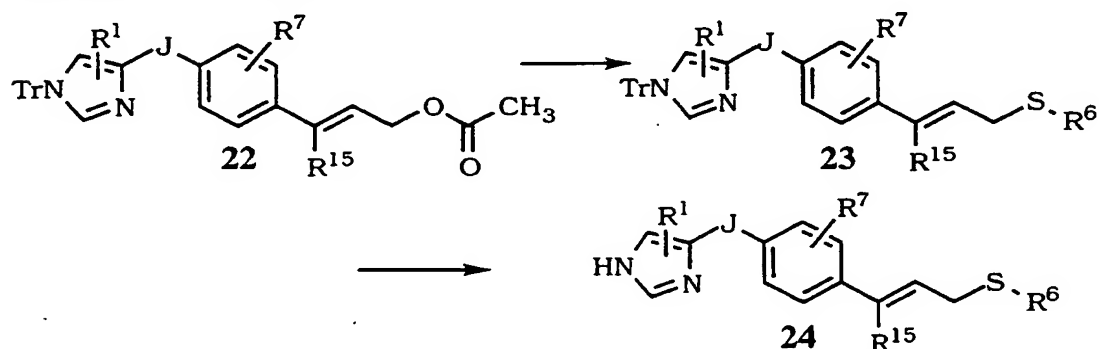
10 Reaction 9 - Amides

The reactions can be run in a manner analogous to that described for preparing the ester above to give the product **19**. Alternatively, the

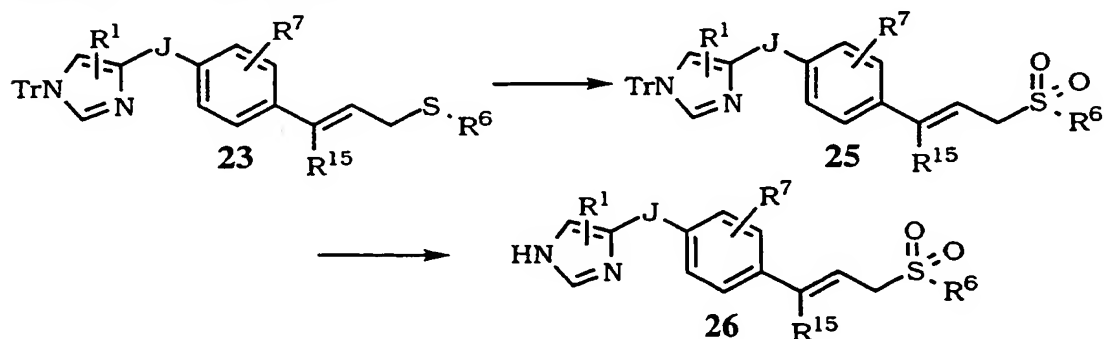
- 15 amine **17** can be coupled with a carboxylic acid R^6CO_2H by treating a solution of **17** in an inert solvent such as methylene chloride with $EDCl$, $HOBT$, NMM , and the acid at a temperature of from $0^\circ C$ to $80^\circ C$ preferably $22^\circ C$.

Reaction 10 - Ureas

These reactions are run in a manner analogous to Step 2 and 3 of the reactions for preparing the carbamates above.

5 Reaction 11 - Sulfides

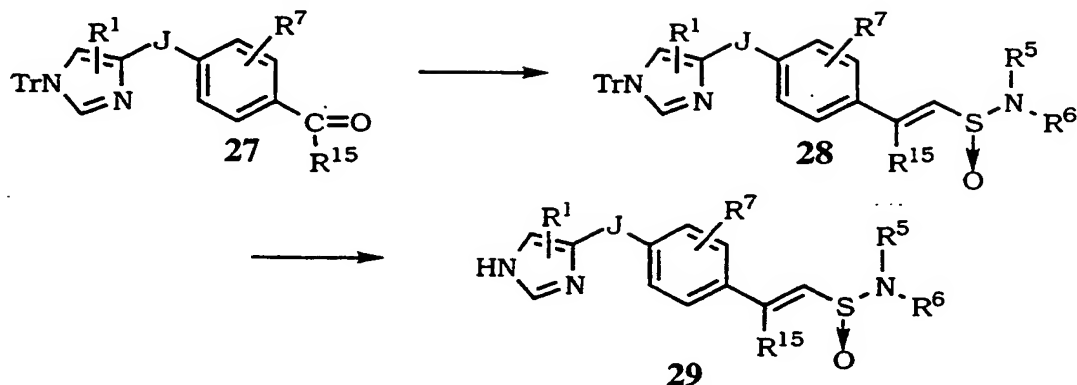
The acetate **22** is reacted with a thiol R⁶SH in a manner similar to that described above for the synthesis of an amine from the acetate to give the sulfide **23** which is deprotected to give the product **24**.

10 Reaction 12 - Sulfones

The sulfide **23** is reacted with a suitable oxidizing agent such as m-CPBA or oxone, preferably oxone, in a suitable organic solvent at a temperature of from 0°C to 80°C, preferably 22°C, to give the sulfone **25**.

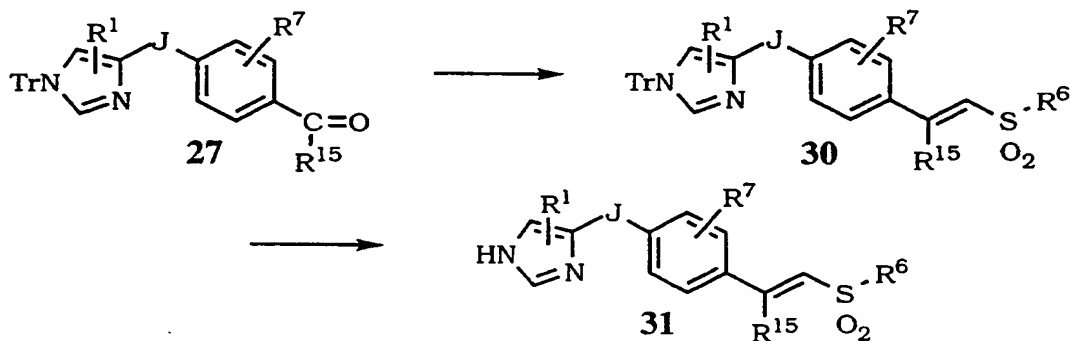
15 Compound **25** is deprotected to give the product

- 20 -

Reaction 13 - -S(O)NR⁵-

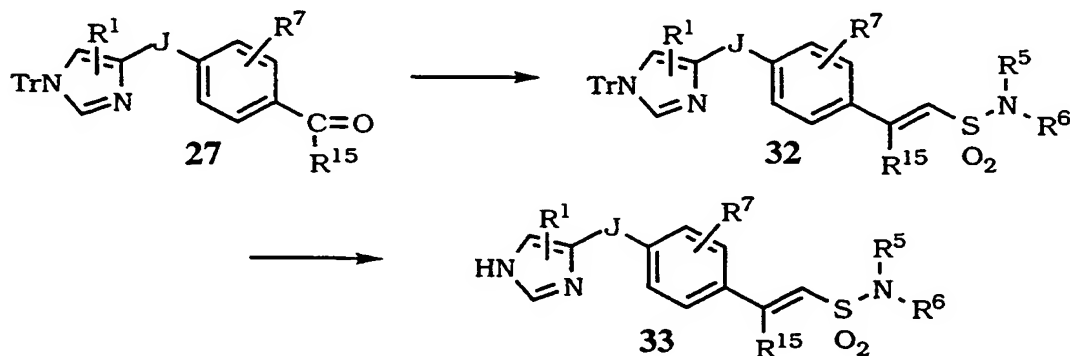
The aldehyde **27** is treated in a similar manner to that described in *Gazz. Chim. Ital.* **1991**, 121, 471 to afford the vinyl sulphenamide **28**.

- 5 Compound **28** is then deprotected to give the target **29**.

Reaction 14 - -SO₂-

The aldehyde **27** is treated in a similar manner to that described in *Ind. J. Chem., Sec B* **1982**, 21B, 208 to afford the vinyl sulphone **30**.

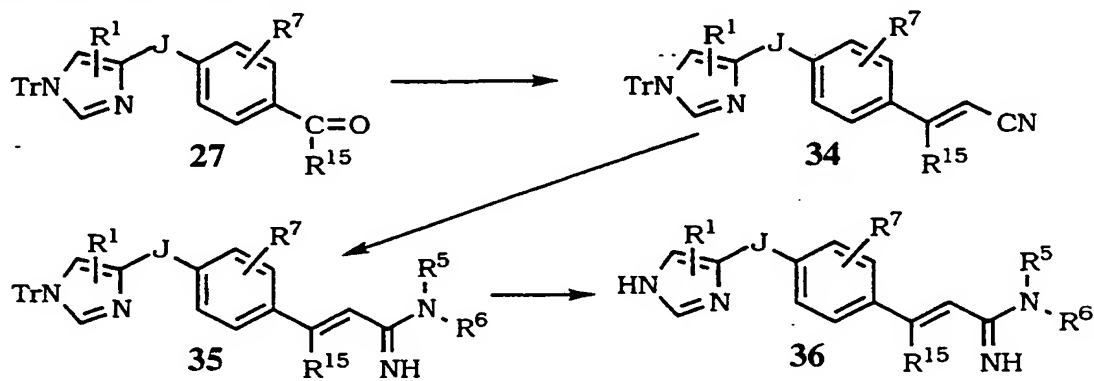
- 10 Compound **30** is then deprotected to give the target **31**.

Reaction 15 - -SO₂ NR⁵-

- 21 -

The aldehyde **27** is treated in a similar manner to that described in *Synthesis* **1975**, 321 to afford the vinyl sulphonamide **32**. Compound **32** is then deprotected to give the target **33**.

Reaction 16 - -C(NH)NR⁵-



5

A solution of diethyl- or dimethylcyanomethyl phosphonate in a suitable organic solvent such as THF, ether, or dioxane, preferably THF, is treated with a strong base such as lithium diisopropylamide, or lithium, sodium or potassium bis(trimethylsilyl)amide at a temperature of from -25°C to about 50°C, preferably 0°C. After 1 hr, the phosphonate carbanion is treated with a solution of the aldehyde **27** in the same solvent. The reaction is stirred at a temperature suitable to complete the reaction and give **34**.

10

Compound **34** is then reacted with the reagent formed by combining equimolar amounts of trimethylaluminum and a suitable amine R⁵R⁶NH in an inert organic solvent such as toluene or xylene, preferably toluene, at a temperature of from 20°C to 130°C preferably 90°C to give compound **35**.

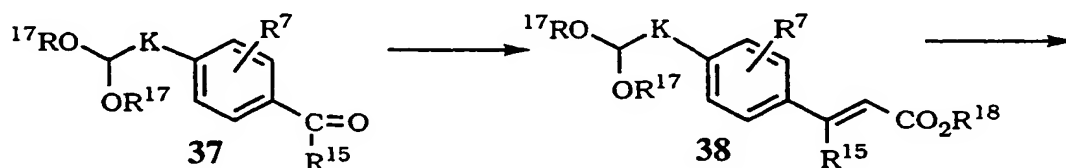
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Deprotection of compound **35** gives the product **36**.

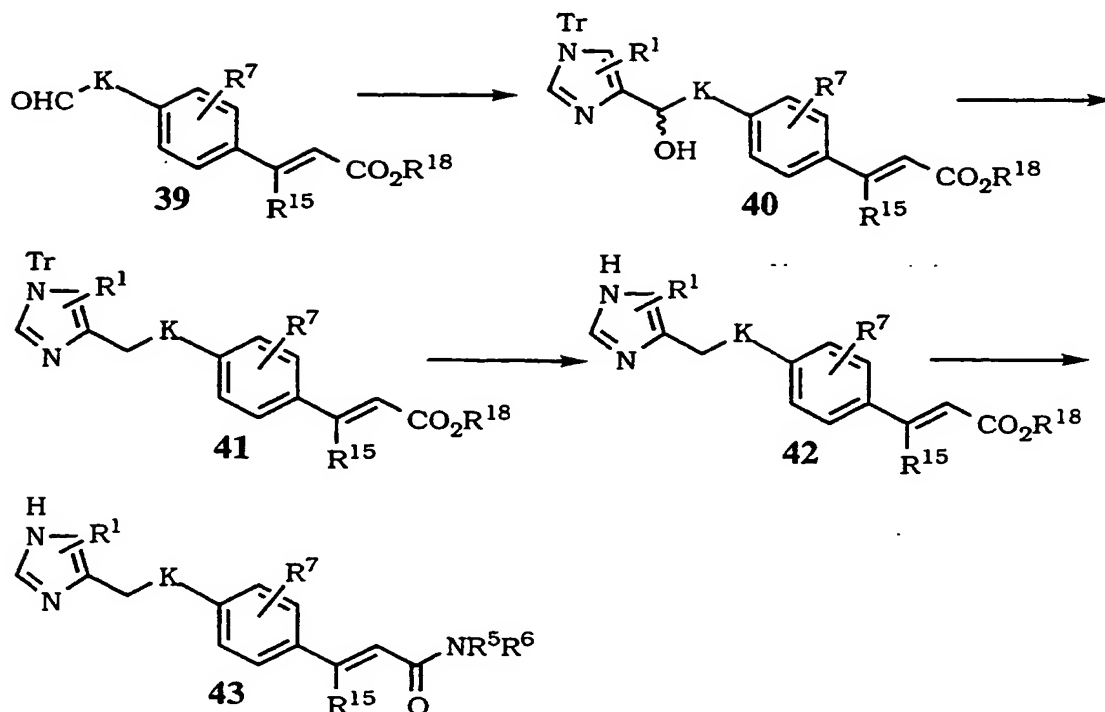
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Reaction 17 - -CONR⁵-

In this reaction scheme K represents (Z)_{n-1}.



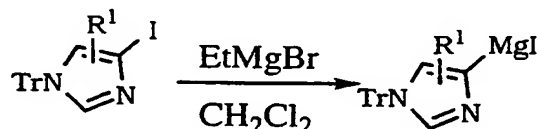
- 22 -



wherein R¹⁸ is lower alkyl, and R¹⁷ is lower alkyl or the two R¹⁷ groups together with the oxygen atoms to which they are bound form a 5 or 6 membered ring.

Triethylphosphonoacetate is treated with a strong base such as LDA or lithium, sodium or potassium bis(trimethylsilyl)amide in an ethereal solvent such as THF, ether, or dioxane, preferably THF, at a temperature from -20°C to 50°C, preferably 0°C. The phosphonate stabilized carbanion is then treated with the carbonyl compound 37 and the mixture stirred at room temperature until the reaction is complete. Other suitable bases include NaH or KH in a polar aprotic solvent such as DMSO or DMF. The product 38 is then deprotected as described above to give the aldehyde 39.

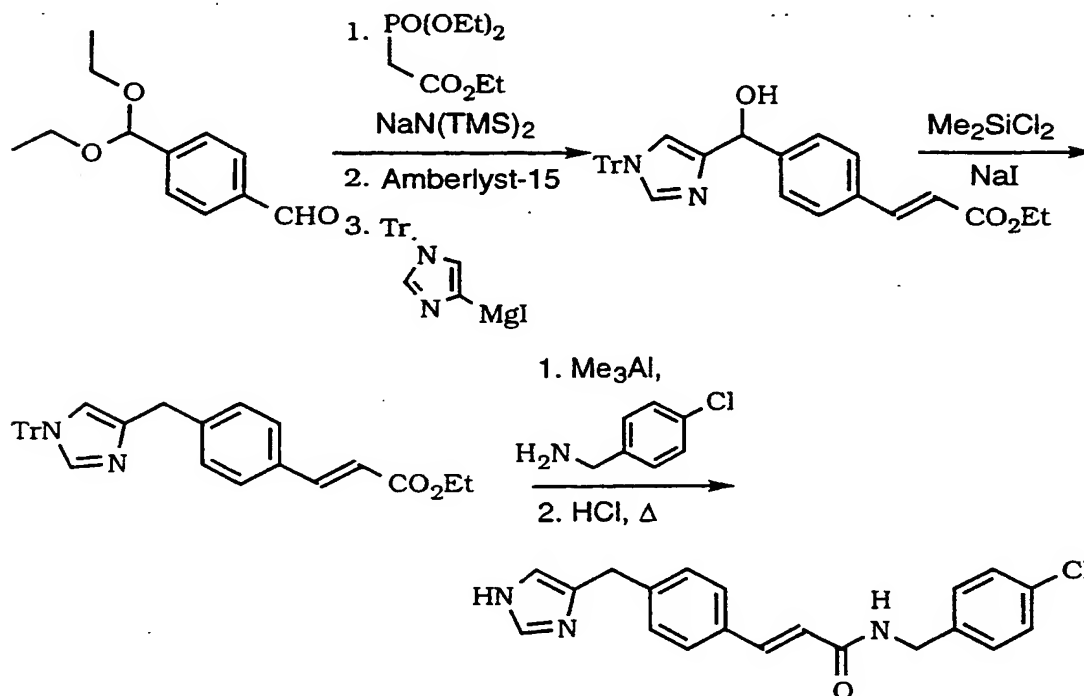
The imidazole compound obtained by the reaction



is then reacted with the aldehyde 39 to give 40 which is reduced to compound 41. Deprotection provides the compound 42 which is then reacted with the amine NHR⁵R⁶ to give the final compound 43.

Compounds useful in this invention are exemplified by the following examples, which should not be construed to limit the scope of the disclosure.

5

EXAMPLE 1Step 1

A solution of 1 M sodium bis(trimethylsilyl)amide in THF (110 ml, 110 mmol) cooled to 0°C was treated with triethylphosphonoacetate (23.5 ml, 118 mmol). After 20 min. the reaction mixture was warmed to RT. and terephthalaldehyde mono-(diethyl acetal) (19.3 ml, 97.0 mmol) dissolved in THF (250 ml) was added over 25 min. The reaction mixture was stirred at 35°C for 3.5 h and concentrated. The residue was suspended in EtOAc (250 ml), washed with H₂O (100 ml) and brine (100 ml), dried with MgSO₄ and concentrated to give 27 g of crude intermediate.

The crude intermediate (27 g) was dissolved in acetone (350 ml) and H₂O (4.5 ml), treated with Amberlyst-15 resin (3.1 g) for 2.5 h, filtered and concentrated to give the aldehyde intermediate.

To a cooled (0°C) solution of 4-iodo-1-trityl imidazole (41.3 g, 96.9 mmol) in CH₂Cl₂ (500 ml) was added 3M EtMgBr (35 ml, 105 mmol) over 15 min. After 30 min. at 0°C the reaction mixture was warmed to RT. and a

- 24 -

solution of the aldehyde intermediate in CH_2Cl_2 (50 ml) was added. After 2 h, the reaction mixture was added to 1 L of half sat. aqueous NH_4Cl .

The organic layer was partitioned off and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 ml). The combined organic layers were washed

- 5 with brine (250 ml), dried with MgSO_4 and concentrated. The product was purified by silica gel chromatography eluting with 1:1 CH_2Cl_2 -EtOAc to give 30.2 g of product (59 mmol, 61 % overall yield): ^1H -NMR (CDCl_3) δ 1.34 (t, $J = 7.1$ Hz, 3H), 4.26 (q, $J = 7.1$ Hz, 2H), 5.79 (s, 1H), 6.40 (d, $J = 16.0$ Hz, 1H), 6.59 (s, 1H), 7.1 - 7.5 (m, 20H), 7.65 (d, $J = 16.0$ Hz, 1H).

10 Step 2

To a solution of the product from Step 1 (10.2 g, 19.9 mmol), CH_2Cl_2 (115 ml), acetone (115 ml) and NaI (11.9 g, 79.3 mmol) was added dichlorodimethylsilane (19.4 ml, 159 mmol). After 15 min. the reaction mixture was added to CH_2Cl_2 (600 ml) and washed with 10%

- 15 aqueous sodium thiosulfate (5 x 400 ml), H_2O (2 x 400 ml) and brine (400 ml), dried with MgSO_4 and concentrated. The product was purified by silica gel chromatography eluting with 2:1 followed by 1:1 CH_2Cl_2 -EtOAc to give 7.2 g of product (14 mmol, 72 % yield). ^1H -NMR (CDCl_3) δ 1.33 (t, $J = 7.0$ Hz, 3H), 3.90 (s, 2H), 4.26 (q, $J = 7.0$, 2H), 6.39 (d, $J = 16.0$ Hz, 1H), 6.58 (s, 1H), 7.1 - 7.5 (m, 20H), 7.65 (d, $J = 16.0$ Hz, 1H).

20

Step 3

To a cooled (0°C) solution of 4-chlorobenzylamine (61 ml, 0.50 mmol) in toluene (2.0 ml) was added 2M trimethyl aluminum in toluene (1.0 ml, 2.0 mmol) in toluene (10 ml) and stirred at RT. for 45 min. To the

- 25 reaction mixture was added a solution of the product from step 2 (0.25 g, 0.50 mmol) in toluene (5.0 ml). After heating at 65°C for 3.5 h, the reaction mixture was cooled, carefully quenched with sat. Na_2SO_4 (aq.), concentrated and purified by silica gel chromatography eluting with 5% NH_3 sat. MeOH in CH_2Cl_2 to give 0.14 g of the amide intermediate (0.23 mmol, 46 % yield).

30

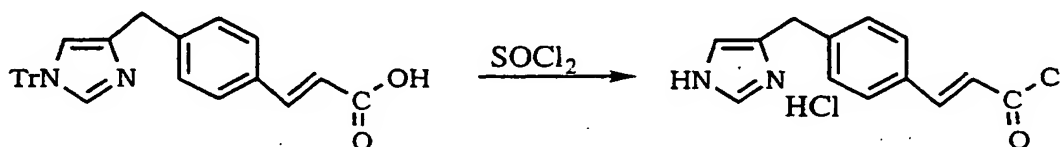
A solution of the amide intermediate (0.14 g, 0.23 mmol) in EtOH (5.0 ml) was treated with 3M HCl (5.0 ml) at 65°C for 3 h and concentrated.

Purification by silica gel chromatography eluting with 5% NH₃ sat. MeOH in CH₂Cl₂ followed by acidification with 3M HCl and concentration gave 42 mg of the titled product (0.11 mmol, 48 % yield). HRMS (M+H⁺): m/e calc'd [C₂₀H₁₉N₃OCl]⁺: 352.1217, found 352.1218.

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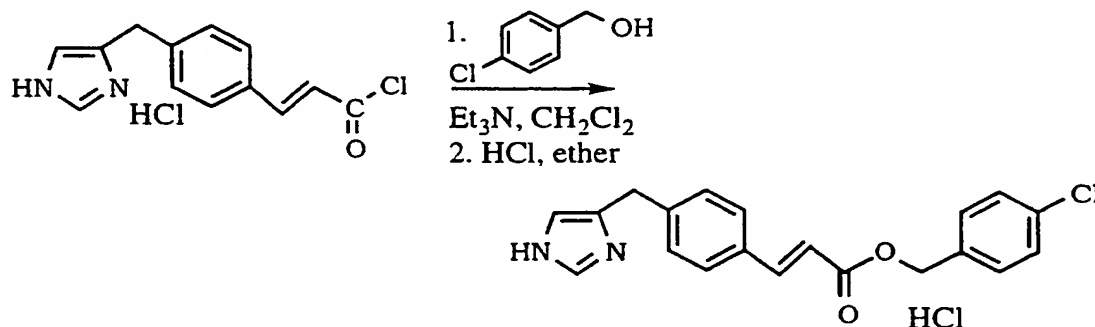
EXAMPLE 2

Step 1.



The acid was suspended in SOCl_2 (20 ml) and stirred for 20 hours at room temperature. The excess SOCl_2 was removed under reduced pressure and the residue dried by azeotropic removal of toluene. The resulting yellow solid was used directly in the next step without purification.

Step 2



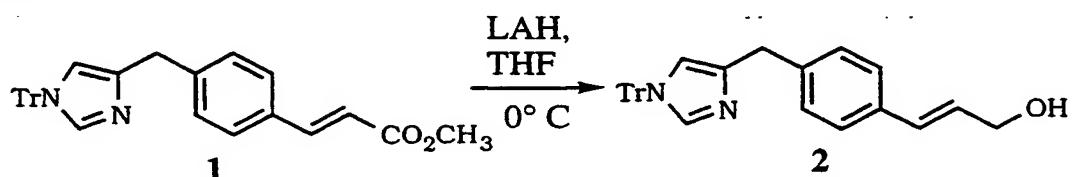
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4-Chlorobenzyl alcohol (0.71 g, 5 mmol) and triethylamine (1.01 g, 10 mmol) were added to a suspension of the acid chloride from Step 1 in dry methylene chloride (15 ml) at 0°C. The reaction mixture was warmed to room temperature and stirred for 24 hours. Additional methylene chloride (50 ml) was added and the organic layer was washed with saturated aqueous NaHCO₃. The organic layer was separated and dried (MgSO₄). Concentration gave an amber oil that was purified on a flash column (97:3 CH₂Cl₂:MeOH/NH₃). A white solid was obtained (0.36 g, 46% from nitrile 4). This material was dissolved in methylene chloride (10

ml) and 1N HCl in ether (5 ml) was added. The solvent was evaporated under a stream of dry argon to give the compound as a white solid.

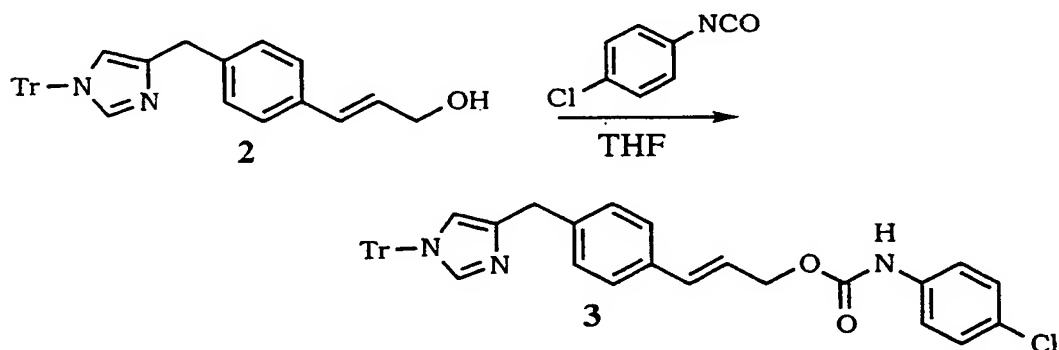
EXAMPLE 3

5 Step 1



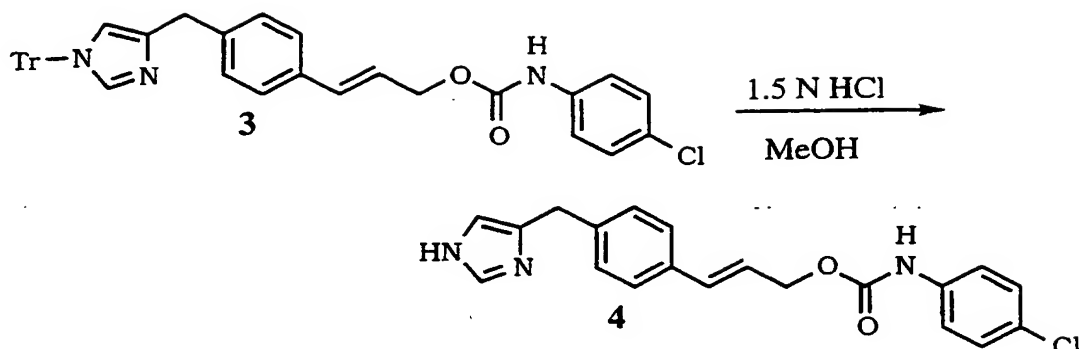
Treat a solution of **1** (4.84 gr., 10 mmol) in dry THF (50 ml) at 0°C and under a nitrogen atmosphere with a solution of LAH in THF (12.5 ml of a 1 M solution, 12.5 mmol). Stir the reaction until TLC indicates the reaction is complete. Dilute the reaction with ether (50 ml) and quench by the addition of saturated aqueous Na₂SO₄. After drying with solid Na₂SO₄, the mixture can be filtered, concentrated, and purified via flash column chromatography to give the product **2**.

Step 2



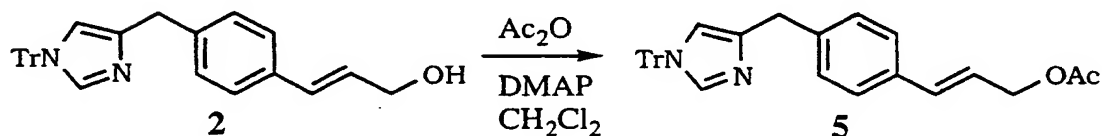
Stir a solution of the alcohol **2** (2.28 gm., 5 mmol) and the isocyanate (0.92 gm., 6 mmol) in dry THF (25 ml) under a nitrogen atmosphere until TLC indicates that the reaction is complete. Remove the THF under reduced pressure, and purify the residue via flash column chromatography to give the product **3**.

- 27 -

Step 3

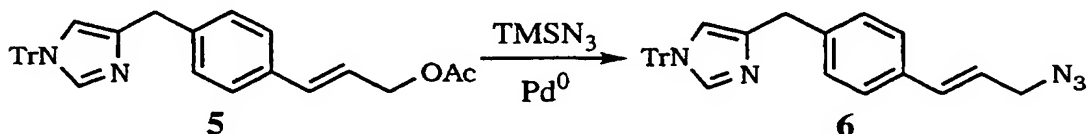
In a manner similar to that described in Example 1, compound 3 (1 gm., 1.6 mmol) may be converted into the product 4.

5

EXAMPLE 4Step 1

Treat a solution of the alcohol 4 (2.28 gm., 5 mmol) and DMAP (61 mg, 0.5 mmol) in dry methylene chloride (20 ml) at 0°C under a nitrogen atmosphere with acetic anhydride (0.61 gm, 6 mmol). Stir the reaction until TLC indicates that it is complete. Dilute the reaction with additional methylene chloride (50 ml) and wash with saturated aqueous NaHCO₃, brine and dry (MgSO₄). Filtration and concentration under reduced pressure gives a residue that can be purified via flash column chromatography to yield the product.

15

Step 2

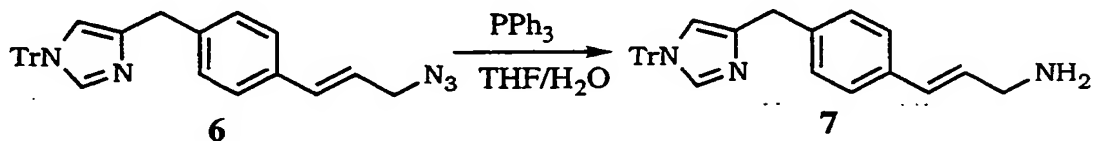
Stir a mixture of dipalladium tris(dibenzylidene acetone) (92 mg, 0.1 mmol), triphenylphosphine (210 mg, 0.8 mmol), trimethylsilyl azide (690 mg, 6 mmol) and compound 5 (1.92 gm, 4 mmol) in dry THF (20 ml) under nitrogen at 50°C until TLC indicates the reaction is complete.

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- 28 -

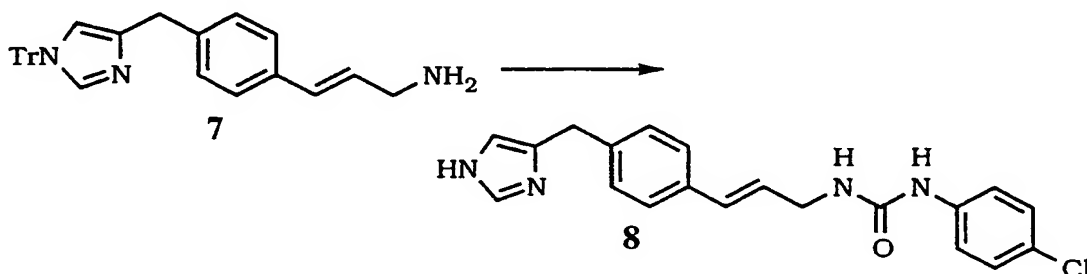
Concentration under reduced pressure gives a residue that can be purified via flash column chromatography to yield the product 6.

Step 3



- 5 Treat a solution of the azide 6 (1.44 gm, 3 mmol) in THF (10 ml) with triphenylphosphine (0.77 gm, 3 mmol) and water (81 mg, 4.5 mmol) and stir until TLC indicates the reaction is complete. The solvent can be removed under reduced pressure and the residue can be purified via flash column chromatography to yield the product 7.

10 Steps 4 and 5

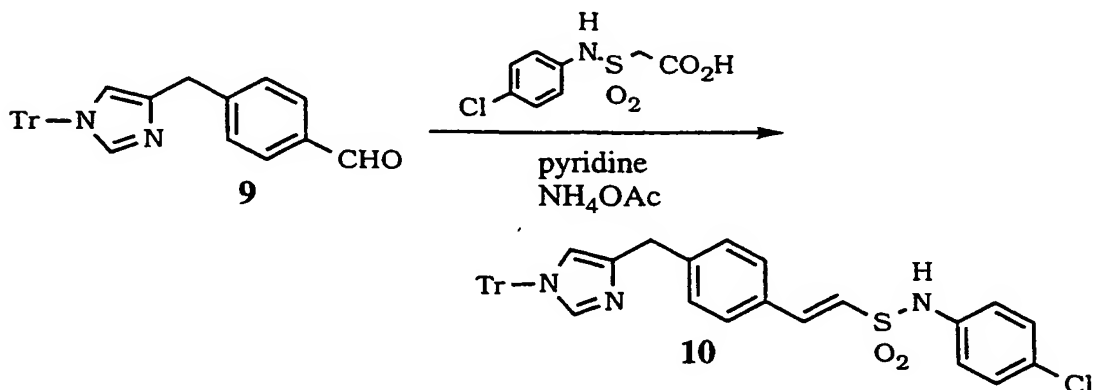


In a manner similar to that described in Example 2 Steps 2 and 3, compound 7 (0.46 gm, 1 mmol) may be converted to the product 8.

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EXAMPLE 5

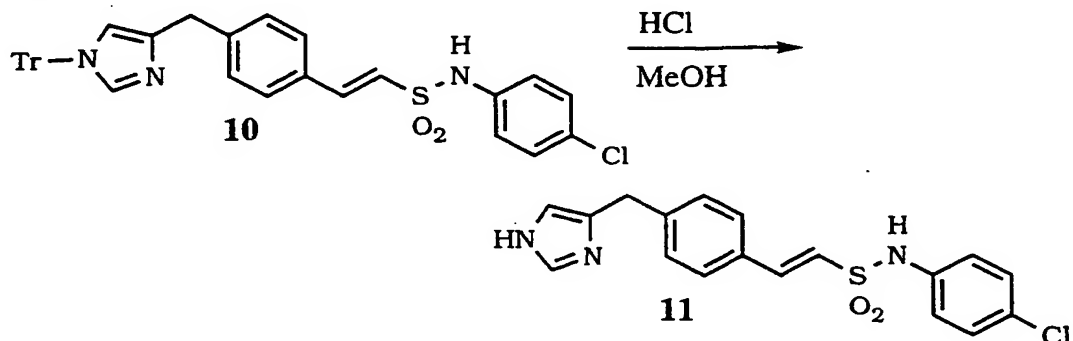
Step 1



- 20 Heat compound 9 (2.14 gm, 5 mmol), ammonium acetate (100 mg), and the sulfonylacetic acid reagent (synthesized according to the

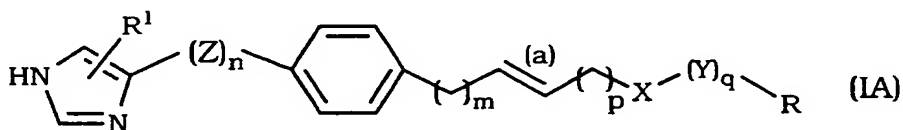
- procedure described in *Synthesis*, 1975, 321; 1.05 gm, 4.2 mmol) at reflux until TLC indicates the reaction is complete. Dilute with methylene chloride (100 ml) and wash with dilute HCl, aqueous NaHCO₃, water, brine and dried (MgSO₄). After filtration and concentration under reduced pressure, the residue can be purified via flash column chromatography to yield the product **10**.

Step 2



- In a manner similar to that described in Example 2 Step 3, compound **10** (0.62 gm, 1 mmol) may be converted to the product **11**.

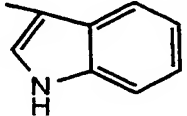
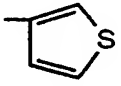
Following the procedures outlined above the compounds ("Com") of formula IA:

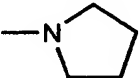

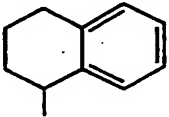
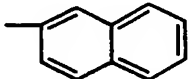
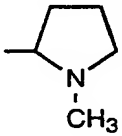


- may be prepared wherein the substituents are defined in the table below.
- In the table R¹ represents the substituent on the imidazole ring. R¹ for the (Z)_n group is H.

Com. No.	n	m	p	q	Y	X	R	R ¹
1	1	0	0	0	-----	CONH	4-chlorophenyl	H
2	1	0	0	1	CH ₂	CONH	4-chlorophenyl	H
3	1	0	0	1	CH ₂ CH ₂	CONH	4-chlorophenyl	H

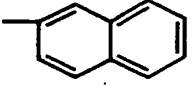
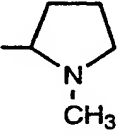
- 30 -

4	1	0	0	0	-----	CON(CH ₃)	4-chlorophenyl	H
5	1	0	0	1	CH ₂ CH ₂	CON(CH ₃)	4-chlorophenyl	H
6	1	0	0	0	-----	CONH ..	phenyl ..	H
7	1	0	0	0	-----	CONH	cyclohexyl	H
8	1	0	0	1	-CH ₂ CH ₂ -	CONH	3-chlorophenyl	H
9	1	0	0	1	CH(CH ₃)CH ₂	CONH	4-chlorophenyl	H
10	1	0	0	1	CH ₂ CH(CH ₃)	CONH	phenyl	H
11	1	0	0	1	CH ₂ CH ₂	CONH	4-methoxy-phenyl	H
12	1	0	0	1	CH ₂ CH ₂	CONH		H
13	1	0	0	0	-----	CONH	4-chlorophenyl	1-CH ₃
14	1	0	0	0	-----	CONH	3-chlorophenyl	1-CH ₃
15	1	0	0	1	CH ₂ CH ₂	CONH		H
16	1	0	0	1	CH ₂ CH ₂	CONH	3-fluorophenyl	H
17	1	0	0	1	CH ₂ CH ₂	CONH	3-pyridyl	H
18	1	0	0	1	CH ₂ CH ₂	CONH	2-fluorophenyl	H
19	1	0	0	1	CH ₂ CH ₂	CONH	2-chlorophenyl	H

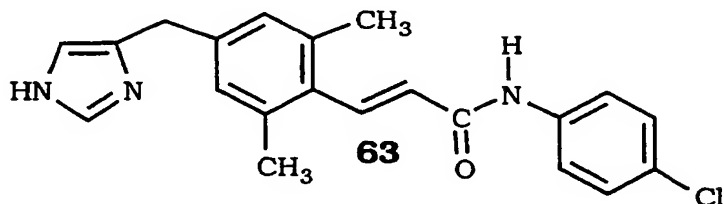
20	1	0	0	1	CH ₂ CH ₂ CH ₂	CONH		H
21	1	0	0	1	CH ₂	CONH		H
22	1	0	0	1	CH ₂ CH ₂	CONH	4-methyl-phenyl	H
23	1	0	0	1	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}(\text{CH}_2)_2 \end{array}$	CONH	phenyl	H
24	1	0	0	0	-----	CONH		H
25	1	0	0	0	-----	CO	4-chlorophenyl	H
26	1	0	0	1	CH ₂	CONH		H
27	1	0	0	1	CH ₂ CH ₂	CONH		H
28	1	0	0	1	CH ₂ CH ₂	CONH	2,4-dichloro-phenyl	H
29	1	0	0	1	CH ₂ CH ₂	CONH	phenyl	H
30	1	0	0	0	-----	CONH	3,5-dichloro-phenyl	H
31	1	0	0	0	-----	CONH	3-chlorophenyl	H
32	1	0	0	0	-----	CONH	3-cyanophenyl	H
33	1	0	0	0	-----	CONH	3-methoxy-phenyl	H

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34	1	0	0	0	-----	CONH	3,5-dimethyl-phenyl	H
35	1	0	0	0	-----	CONH	3-fluorophenyl	H
36	1	0	0	0	-----	CONH	4-fluorophenyl	H
37	1	0	0	0	-----	CONH	3-trifluoro-methoxy-phenyl	H
38	1	0	0	0	-----	CONH	4-trifluoro-methoxy-phenyl	H
39	1	0	1	0	-----	NHCONH	3,5-dimethyl-phenyl	H
40	1	0	1	0	-----	NHCONH	3-fluorophenyl	H
41	1	0	1	0	-----	NHCONH	4-fluorophenyl	H
42	1	0	1	0	-----	NHCONH	3-trifluoro-methoxy-phenyl	H
43	1	1	1	0	-----	NHCONH	4-trifluoro-methoxy-phenyl	H
44	1	1	1	0	-----	NHCONH	3-methoxy-phenyl	H
45	1	1	1	0	-----	NHCONH	3,5-dimethyl-phenyl	H
46	1	1	1	0	-----	NHCONH	3-fluorophenyl	H
47	1	1	1	0	-----	NHCONH	4-fluorophenyl	H

48	1	1	1	0	-----	NHCONH	3-trifluoro-methoxy-phenyl	H
49	1	0	1	0	-----	NHCONH	4-trifluoro-methoxy-phenyl	H
50	2	0	1	1	CH ₂	OCONH		H
51	2	1	1	1	CH ₂ CH ₂	OCONH		H
52	1	0	1	1	CH ₂ CH ₂	OCONH	2,4-dichloro-phenyl	H
53	1	0	1	1	CH ₂ CH ₂	OCONH	phenyl	H
54	1	0	0	0	-----	COO	3-methoxy-phenyl	H
56	1	0	0	0	-----	N(CH ₃)	3,5-dimethyl-phenyl	H
57	1	0	0	0	-----	NH	3-fluorophenyl	H
58	1	0	0	0	-----	SO ₂ NH	4-fluorophenyl	H
59	1	0	0	0	-----	C(NH)NH	3-trifluoro-methoxy-phenyl	H
60	1	0	0	0	-----	S	4-trifluoro-methoxy-phenyl	H
61	1	0	0	0	-----	CONH	4-chlorophenyl	H
62	1	0	0	0	-----	C(NH)NH	4-chlorophenyl	H

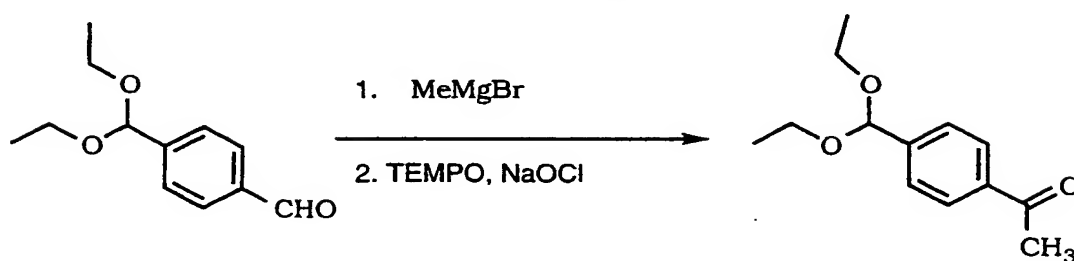
Also, following the above procedures compound **63**:



was prepared.

5

EXAMPLE 66

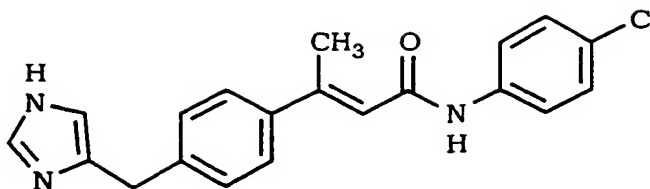


A solution of terephthalaldehyde mono-(diethyl acetal) (5.0 ml, 25 mmol) in THF (100 ml) was treated with 1.4 M MeMgBr (21.5 ml, 30 mmol). After 30 min, the reaction mixture was added to water (200 ml) and extracted with EtOAc (200 ml). The organic layer was washed with brine (100 ml), dried with Na₂SO₄ and concentrated to give the crude alcohol intermediate as a colorless oil.

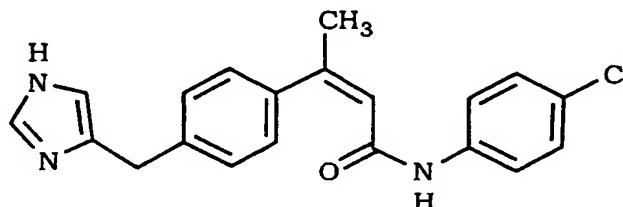
To a 0°C solution of the crude alcohol intermediate dissolved in EtOAc (150 ml) was added a solution of NaBr (2.60 g, 25.3 mmol) in sat. aq. NaHCO₃ (150 ml) and TEMPO (39 mg, 0.25 mmol). While rapidly stirring the reaction mixture, 0.7 M aq. NaOCl (36 ml, 25 mmol) was added over 20 min then sat. Na₂S₂O₃ (50 ml). After warming to RT, the reaction mixture was partitioned and the aqueous layer was extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with brine (100 ml), dried with Na₂SO₄ and concentrated to give 4.86 g of the ketone product (21.9 mmol, 87 % yield for two steps) as a yellow oil.

Following a procedure similar to that of Example 1, the ketone was converted to the final product. The (E) isomer:

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and the (Z) isomer:



of the final product were obtained.

5 The data for these two isomers were:

(E)-N-(4-chlorophenyl)-3-[4-[(1H-imidazol-4-yl)methyl]-phenyl]-3-methyl-2-propenamide: $^1\text{H-NMR}$ (CD_3OD) δ 2.64 (s, 3H), 4.03 (s, 2H), 6.43 (s, 1H), 6.88 (s, 1H), 7.35 (d, $J = 8$ Hz, 2H), 7.37 (d, $J = 9$ Hz, 2H), 7.57 (d, $J = 8$ Hz, 2H), 7.68 (s, 1H), 7.70 (d, $J = 9$ Hz, 2H); HRMS ($\text{M}+\text{H}^+$): m/e calc'd [$\text{C}_{20}\text{H}_{19}\text{N}_3\text{OCl}$] $^+$: 352.1217, found 352.1214.

(Z)-N-(4-chlorophenyl)-3-[4-[(1H-imidazol-4-yl)methyl]-phenyl]-3-methyl-2-propenamide: $^1\text{H-NMR}$ (CD_3OD) δ 2.27 (s, 3H), 3.99 (s, 2H), 6.16 (s, 1H), 6.83 (s, 1H), 7.4 (m, 6H), 7.43 (d, $J = 8$ Hz, 2H), 7.65 (s, 1H); HRMS ($\text{M}+\text{H}^+$): m/e calc'd [$\text{C}_{20}\text{H}_{19}\text{N}_3\text{OCl}$] $^+$: 352.1217, found 352.1227.

15

Mass Spectral Data of Compounds:

Compound #	Calculated	Found	Compound #	Calculated	Found
1	338.1060	338.1066	19	366.1373	366.1372
2	352.1217	352.1218	21	308.1399	308.1405
3	366.1373	366.1372	22	346.1919	346.1916
4	352.1217	352.1214	23	360.2076	360.2074
5	380.1530	380.1525	24	358.1919	358.1924
6	304.1540	304.1449	26	368.1763	368.1763
7	310.1919	310.1917	28	400.0983	400.0993
8	366.1373	366.1371	29	FAB = 332 (M + 1)	
9	380.1530	380.1532	30	372.0670	372.0673
10	346.1919	346.1924	31	338.1060	338.1069
11	362.1869	362.1862	32	329.1402	329.1402
12	371.1872	371.1875	33	334.1556	334.1559
15	338.1327	338.1331	35	322.1356	322.1356
16	350.1669	350.1667	36	322.1356	322.1356
17	333.1715	333.1720	37	388.1273	388.1274
18	350.1669	350.1670	38	388.1273	388.1270
-----	-----	-----	39	332.1763	332.1762

Additional mass spectral data are: (1) Compound No. 61 - CI 352 (M+1); and (2) Compound No. 62 - FAB 337 (M+1).

5

H₃ Receptor Binding Assay

The source of the H₃ receptors in this experiment was guinea pig brain. The animals weighed 400-600 g. The brain tissue was homogenized using a Polytron in a solution of 50 mM Tris, pH 7.5. The final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1,000 x g for 10 min. in order to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to sediment the membranes, which were next washed three times in homogenization buffer (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

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All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was 2 μ g/ml with 0.1% DMSO. Membranes were then added (400 μ g of protein) to the reaction tubes. The reaction was started
5 by the addition of 3 nM [3 H]R- α -methylhistamine (8.8 Ci/mmol) or 3 nM [3 H]N $^{\alpha}$ -methylhistamine (80 Ci/mmol) and continued under incubation at 30°C for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitated by liquid scintillation spectrometry. All incubations were
10 performed in duplicate and the standard error was always less than 10%. Compounds that inhibited more than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K_i (nM).

Compounds 1-13, and 15-38 had a K_i in the range of 1-1000 nM.
15 Compounds 1, 3, 6, 8-11, 15, 16, 18, 19, 22, and 29-38 had a K_i in the range of 1-19 nM.

From these test results and the background knowledge about the compounds described in the references in the section "Background of the Invention", it is to be expected that the compounds of the invention would
20 be useful in treating inflammation, allergy, diseases of the GI-tract, cardiovascular disease, or disturbances of the central nervous system.

Pharmaceutically acceptable inert carriers used for preparing pharmaceutical compositions from the compounds of Formula I and their salts can be either solid or liquid. Solid form preparations include
25 powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may comprise from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid
30 dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions and emulsions, for example water or water-propylene glycol solutions for

parenteral injection. Liquid form preparations may also include solutions for intranasal administration.

Also included are solid form preparations which are intended for conversion, shortly before use, into liquid form preparations for either oral
5 or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

10 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into conveniently sized molds, and allowed to cool and thereby solidify.

15 Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose. The quantity of active compound in a unit
20 dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 500 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated.
25 The determination of the proper dosage for a particular condition is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may
30 be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of

the symptoms being treated. A typical recommended dosage regimen is oral administration of from 1 mg to 2000 mg/day, preferably 10 to 1000 mg/day, in one to four divided doses to achieve relief of the symptoms. The compounds are non-toxic when administered at therapeutic doses.

- 5 The following are examples of pharmaceutical dosage forms which contain a compound of the invention. As used therein, the term "active compound" is used to designate one of the compounds of the formula I or salt thereof, especially compounds 6 and 29 herein (as free base), namely N-[(4-chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene
- 10 methanimidamide and N-[(4-chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene ethanimidamide, or the dihydrochloride thereof, but any other compound of the formula I or salt thereof can be substituted therefor:

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

<u>No.</u>	<u>Ingredients</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	<u>3</u>	<u>7</u>
	Total	300	700

15 Method of Manufacture

- Mix Items No. 1 and 2 in a suitable mixer for 10 to 15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for
- 20 10–15 minutes. Add Item No. 5 and mix for 1 to 3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

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EXAMPLE BCapsules

<u>No.</u>	<u>Ingredient</u>	<u>mg/capsule</u>	<u>mg/capsule</u>
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	<u>4</u>	<u>7</u>
	Total	250	700

Method of Manufacture

Mix Items No. 1, 2 and 3 in a suitable blender for 10 to 15 minutes.

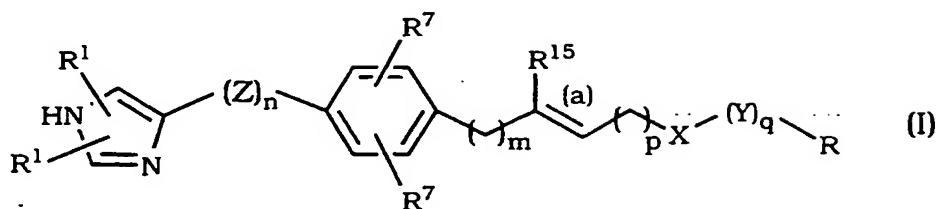
- 5 Add Item No. 4 and mix for 1 to 3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While a number of embodiments of this invention are described herein, it is apparent that the embodiments can be altered to provide other embodiments that utilize the compositions and processes of this invention.

- 10 Therefore, it will be appreciated that the scope of this invention includes alternative embodiments and variations which are defined in the foregoing Specification and by the Claims appended hereto; and the invention is not to be limited to the specific embodiments that have been presented herein by way of example.

WHAT IS CLAIMED IS:

1. A compound of the formula:



- 5 or a pharmaceutically acceptable salt or solvate thereof, wherein:
- the double bond (a) is E or Z;
- each R¹ is independently selected from the group consisting of hydrogen, lower alkyl, trihalomethyl, phenyl and benzyl;
- each R⁷ is independently selected from the group consisting of
- 10 hydrogen, lower alkyl, halogen, trihalomethyl, NR¹⁰R¹¹, or a group OR¹⁰, whereby R¹⁰ and R¹¹ are independently selected from hydrogen, lower alkyl or trihalomethyl;
- X is -CONR⁵-, -SO₂-, -S-, -CO-, -COO-, -CN(OR⁵)NR⁵-, -C(NR⁵)NR⁵-, -SONR⁵-, -SO₂NR⁵- and, provided p is not zero, X may also
- 15 be -O-, -NR⁵-, -NR⁵CONR⁵-, -OCONR⁵-, -O-CO- or -NR⁵CO-;
- Y is C₁-C₃-alkyl, optionally substituted at any carbon atom of the group by one substituent R⁵;
- Z is C(R¹)₂; wherein no more than two R¹ groups are other than hydrogen;
- 20 n is 1 or 2;
- m is 0 or 1;
- p is 0 or 1;
- q is 0 or 1;
- R is selected from:
- 25 (1) C₃ to C₇ cycloalkyl,
- (2) heterocyclic groups,
- (3) aryl,
- (4) heteroaryl,

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- (5) substituted C₃ to C₇ cycloalkyl having 1-3 substituents independently selected from the group consisting of lower alkyl trihalomethyl and NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are independently selected from hydrogen, lower alkyl or trihalomethyl,
- 5 (6) substituted heterocyclic having 1-3 substituents independently selected from the group consisting of lower alkyl trihalomethyl and NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ as defined above, said substituents being bound to carbon atoms in the ring such that the total number of substituents in the ring is 1 to 3; and wherein the heterocyclic
- 10 ring contains substitutable nitrogen atoms, said nitrogen atoms are optionally substituted with lower alkyl;
- (7) substituted aryl having 1-3 substituents independently selected from the group consisting of lower alkyl, halogen, trihalomethyl, CN, NO₂, OR¹⁰ or NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ as defined above,
- 15 (8) substituted heteroaryl having 1-3 substituents independently selected from the group consisting of lower alkyl, halogen, trihalomethyl, CN, NO₂, OR¹⁰ or NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are as defined above; and
- each R⁵ independently represents hydrogen, lower alkyl or poly-
- 20 halo-loweralkyl.
2. The compound of Claim 1 wherein both R⁷ are hydrogen.
3. The compound of Claim 2 wherein n is 1.
- 25 4. The compound of Claim 3 wherein R¹ is hydrogen and R is selected from: (1) phenyl substituted by one or two substituents selected from; lower alkyl, halogen, trihalomethyl, CN, NO₂, OR¹⁰ or NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ as defined above, or (2) pyridyl substituted by one or
- 30 two substituents selected from: lower alkyl, halogen, trihalomethyl, CN, NO₂, OR¹⁰ or NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ as defined above.

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5. The compound of Claim 4 wherein R represents phenyl substituted by or pyridyl substituted by one or two substituents selected from: halogen, methoxy, CF_3 , CN or OCF_3 .

5 6. The compound of Claim 5 wherein R is (1) mono-substituted phenyl wherein said substituent is in the 3- or the 4-position or (2) a di-substituted phenyl wherein the two substituents are the same and are in the 3,5-positions.

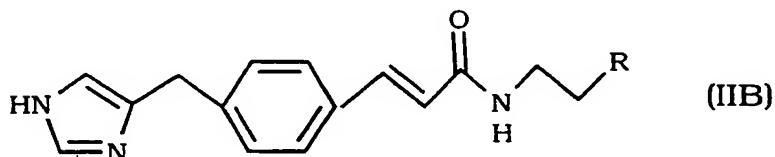
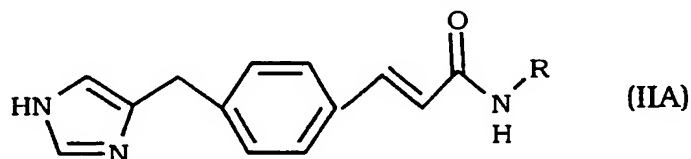
10 7. The compound of Claim 6 wherein X is selected from $-\text{CONR}^5$, $-\text{NH}-$, $-\text{SO}_2-$, $-\text{O}-$ or $-\text{SO}_2\text{NH}-$.

8. The compound of Claim 7 wherein X is $-\text{CONR}^5$ and m is 0.

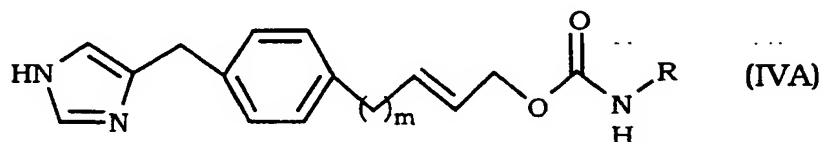
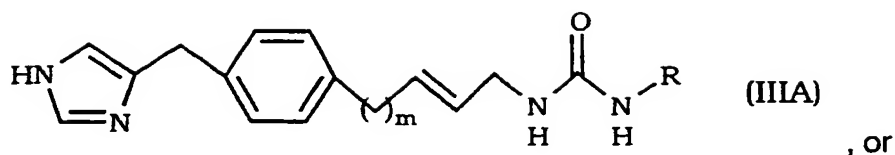
15 9. The compound of Claim 8 wherein (1) p is 0 and (2) q is 0 or 1, wherein when q is 1, then Y represents $-\text{CHR}^5\text{CHR}^5-$ wherein one R^5 is hydrogen.

20 10. The compound of Claims 5, 7 or 9 wherein said substituent is chlorine or fluorine.

11. The compound of Claim 1 selected from:

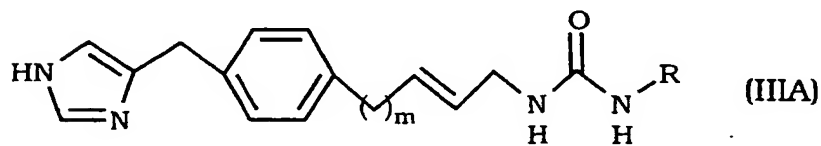
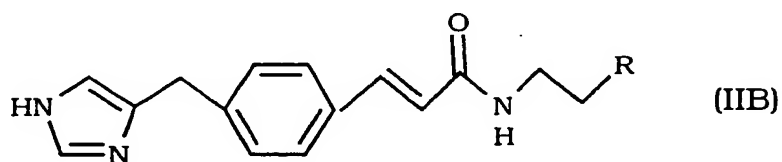
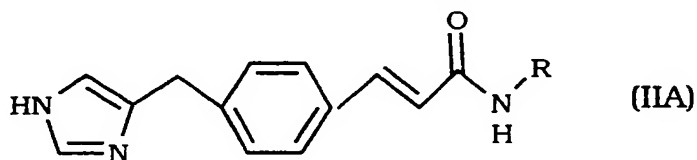


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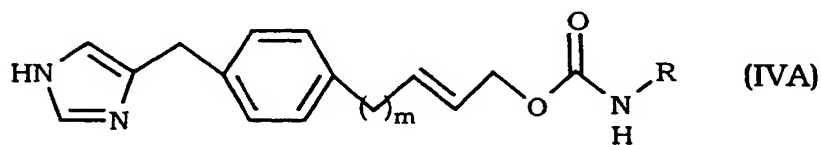


- 5 12. The compound of Claim 11 wherein R is (1) mono-substituted phenyl wherein said substituent is in the 3- or the 4-position or (2) a di-substituted phenyl wherein the two substituents are the same and are in the 3,5-positions.

- 10 13. The compound of Claim 7 selected from:



or



15

- 45 -

wherein m is 0 or 1, and R is selected from (1) phenyl, (2) 4-Cl-phenyl, (3) 3,5-dimethylphenyl, (4) 3-F-phenyl, (5) 4-F-phenyl, (6) 3-methoxyphenyl or (7) 3-CN-phenyl.

5 14. The compound of Claim 7 wherein X is -NH-, -SO₂-, -O- or -SO₂NH-, and R is (1) phenyl, (2) phenyl substituted in the 3-or 4-position by Cl, F, CN or OCH₃, or (3) phenyl substituted in the 3- and 5- positions by Cl, F, CF₃, CH₃, OCH₃ or OCF₃.

10 15. The compound of Claim 14 wherein (1) m is 0 or 1, (2) p is 1 and (3) q is 0 or 1, wherein when q is 1 then Y represents -CH₂CH₂-.

 16. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof, in
15 combination with a pharmaceutically acceptable carrier or excipient.

 17. A method of treating allergy, inflammation, cardiovascular disease, hypotension, glaucoma, sleeping disorders, diseases of the GI-tract, states of hyper and hypo motility of the gastrointestinal tract, or
20 disturbances of the central nervous system, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines, comprising administering an effective amount of a compound, or a salt or solvate thereof, of Claim 1, or a pharmaceutically acceptable acid addition salt or solvate thereof, to a patient in need of such treatment.

25 18. A method for treatment of upper airway allergic responses comprising administering to a patient in need of such treatment a compound, or a salt or solvate thereof, of Claim 1 in combination or admixture with a histamine H₁ receptor antagonist.

30 19. The method of Claim 18 wherein said H₁ antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine, cetirizine.

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20. The method of Claim 19 wherein said H₁ antagonist is selected from: loratadine or descarboethoxyloratadine.

21. The use of a compound, or a salt or solvate thereof, of Claim 1 for the manufacture of a medicament for use in treating allergy, inflammation, cardiovascular disease, hypotension, glaucoma, sleeping disorders, diseases of the GI tract, states of hyper and hypo motility of the gastrointestinal tract, disturbances of the central nervous system, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines.

22. The use of a compound, or a salt or solvate thereof, of Claim 1 for the manufacture of a medicament for use in combination with a medicament manufactured for use as an histamine H₁ receptor antagonist, said combination for use in the treatment of upper airway allergic responses.

23. The use of Claim 22 wherein said H₁ antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine, cetirizine.

24. The use of Claim 22 wherein said H₁ antagonist is selected from: loratadine or descarboethoxyloratadine.

25. The use of a compound, or a salt or solvate thereof, of Claim 1 treating allergy, inflammation, cardiovascular disease, hypotension, glaucoma, sleeping disorders, diseases of the GI tract, states of hyper and hypo motility of the gastrointestinal tract, disturbances of the central nervous system, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines.

26. The use of a compound, or a salt or solvate thereof, of Claim 1 in combination with a an histamine H₁ receptor antagonist for the treatment of upper airway allergic responses.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23225

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D233/64 A61K31/415 C07D409/12 C07D405/12 C07D403/12
C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 14007 A (SCHERING CORPORATION) 26 May 1995 cited in the application see claims	1-17
A	WO 93 14070 A (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MEDICALE) 22 July 1993 see claims	1-17
A	WO 96 29315 A (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MEDICALE) 26 September 1996 see claims	
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 January 1999

Date of mailing of the international search report

10/02/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23225

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 06394 A (SCHERING CORPORATION) 19 February 1998 cited in the application see the whole document -----	18-26

INTERNATIONAL SEARCH REPORT

international application No.

PCT/US 98/23225

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1. ☒ Claims Nos.: 17-20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 17-20
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
- 2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
- 3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- 1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
- 2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
- 3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
- 4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23225

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WO 9806394 A	19-02-1998	AU 3973397 A	06-03-1998

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 Docket No. DEAV2003/0011US NP
PRIOR ART